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(71) Applicant: BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US).

(72) Inventors: BEHOUNEK, Bruce, D.; 1405 Bridle Court, Yardley, PA 19067 (US). MCGOVERN, Mark, E.; The Floridian, Penthouse #3, 650 West Avenue, Miami Beach, FL 33139 (US). BELDER, Rene; 62 Cherry Brook Drive, Princeton, NJ 08540 (US).

(74) Agents: RODNEY, Burton et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

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(54) Title: METHOD FOR TREATING ATHEROSCLEROSIS WITH AN MPT INHIBITOR AND CHOLESTEROL LOWERING DRUGS

(57) Abstract

A method is provided for preventing or reducing the risk of onset of a cardiovascular event by administering an MTP inhibitor alone or in combination with another cholesterol lowering drug such as an HMG CoA reductase inhibitor such as pravastatin, to a patient who may or may not have one or more risk factors for a coronary and/or cerebrovascular event such as hypercholesterolemia.

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METHOD FOR TREATING ATHEROSCLEROSIS WITH AN MPT INHIBITOR AND CHOLESTEROL LOWERING DRUGS

Field of the Invention

The present invention relates to a method for preventing or reducing the risk of or onset of cardiovascular events employing an MTP inhibitor alone or in combination with another cholesterol lowering drug, for example, an HMG CoA reductase inhibitor, such as pravastatin.

Background of the Invention

Despite significant progress in reducing mortality due to atherosclerotic coronary artery disease (CAD) over the last several years, cardiovascular disease remains the major cause of death in most developed countries. The relation between CAD and elevated concentrations of serum total cholesterol, particularly low-density lipoprotein (LDL) cholesterol, is well documented.

It is well established that lipid disorders are important factors in the development of coronary heart disease (CHD), Schettler, G., "The role of diet and drugs in lowering serum cholesterol in the postmyocardial infarction patient," Cardiovasc. Drugs Ther., 1989, 2/6 (795-799).

Glatter, T.R., "Hyperlipidemia. What is 'normal', who should be treated and how," Postgrad. Med., 1984, 76/6 (49-59), states that "As the Coronary Primary Prevention Trial has recently shown, a 1% reduction in cholesterol level produces a 2% reduction in risk of myocardial infarction."

Goldstein, J.L., et al, "The LDL receptor defect in familial hypercholesterolemia. Implications for pathogenesis and therapy," Med. Clin. North Am., 1982, 66/2 (335-362) indicate that "familial hypercholesterolemia was

the first genetic disorder recognized to cause myocardial infarction. To this day, it remains the outstanding example of a single-gene mutation that causes both hypercholes-terolemia and coronary atherosclerosis."

Satler, L.F., et al, "Reduction in coronary heart disease: Clinical and anatomical considera-tions," Clin. Cardiol., 1989, 12/8 (422-426) disclose that "the higher the total plasma cholesterol and low density lipoprotein cholesterol (LDL-C), the greater the risk that coronary artery disease will develop. Recently, clinical trials including the Coronary Drug Project, the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), and the Helsinki Heart Study provided evidence that lowering cholesterol reduces the frequency of fatal and nonfatal coronary events." In addition, Satler et al disclose that other studies "demonstrated that lowering of cholesterol was associated with a decreased incidence of progression of coronary disease, as well as with the potential for reduction in the atherosclerotic plaque."

Wilhelmsen, L., "Practical guidelines for drug therapy after myocardial infarction," Drugs, 1989, 38/6 (1000-1007) discloses that it is advisable to correct blood lipid disturbances in effective management of the postinfarction patient.

Yamamoto, A., et al, "Clinical features of familial hypercholesterolemia," Arteriosclerosis, Jan.-Feb. 1989, 9 (1 Suppl.) p I66-74, disclose that "in addition to the low density lipoprotein (LDL) cholesterol level, higher triglyceride and lower high density lipoprotein (HDL) cholesterol levels correlate with an increased risk of ischemic heart disease.

Other references disclosing the relation between CAD and elevated concentrations of serum total cholesterol include

1. Canner P.L. et al, "Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin", J. Am. Coll. Cardiol. 1986; 8:1245-1255.

2. Frick, M.H. et al, "Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease," N. Engl. J. Med. 1987; 317:1237-1245.

3. Kannel, W.B. et al, "Serum cholesterol, lipoproteins, and the risk of coronary heart disease: the Framingham Study," Ann. Intern. Med. 1971; 74:1-12.

4. "The Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results, I: reduction in incidence of coronary heart disease," JAMA 1984; 251-351-364.

5. Martin, M.J. et al, "Serum cholesterol, blood pressure, and mortality: implications from a cohort of 361,662 men," Lancet 1986; 2:933-936.

Efforts to further reduce the mortality rate from CAD should benefit from appropriate screening for, and treatment of, hypercholesterolemia. Primary hypercholesterolemia is initially treated with a low-cholesterol low-fat diet and lifestyle modification. If these measures are inadequate, lipid lowering drugs are then added. Agents currently available for the treatment of hypercholesterolemia include bile acid-binding resins, nicotinic acid, probucol, fibrates, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Pravastatin, a member of the latter class, in doses up to 40 mg/day, reduces serum LDL cholesterol an average of 32 to 34% and total cholesterol an average of 24 to 26% in patients with primary hypercholesterolemia. Hunninghake, D.B. et al, "Efficacy and safety of pravastatin in patients with primary hypercholesterolemia, I: a dose-response study." Atherosclerosis 1990; 85:81-89.

European Patent Application 0461548A2 discloses use of an HMG CoA reductase inhibitor for preventing a second heart attack.

Pending U.S. Application Serial No. 08/424,984 filed April 19, 1995, discloses use of an HMG CoA reductase

inhibitor for preventing a second heart attack in patients having normal cholesterol.

U.S. application Serial No. 08/212,470 filed March 11, 1994, disclosed use of pravastatin to slow progression of coronary artery atherosclerosis.

U.S. application Serial No. 08/182,471 filed January 18, 1994, discloses a method for preventing or reducing risk of or onset of cardiovascular events employing an HMG CoA reductase inhibitor.

The microsomal triglyceride transfer protein (MTP) catalyzes the transport of triglyceride (TG), cholesteryl ester (CE), and phosphatidylcholine (PC) between small unilamellar vesicles (SUV). Wetterau & Zilversmit, Chem. Phys. Lipids 38, 205-22 (1985). When transfer rates are expressed as the percent of the donor lipid transferred per time, MTP expresses a distinct preference for neutral lipid transport (TG and CE), relative to phospholipid transport. The protein from bovine liver has been isolated and characterized. Wetterau & Zilversmit, Chem. Phys. Lipids 38, 205-22 (1985). Polyacrylamide gel electrophoresis (PAGE) analysis of the purified protein suggests that the transfer protein is a complex of two subunits of apparent molecular weights 58,000 and 88,000, since a single band was present when purified MTP was electrophoresed under nondenaturing condition, while two bands of apparent molecular weights 58,000 and 88,000 were identified when electrophoresis was performed in the presence of sodium dodecyl sulfate (SDS). These two polypeptides are hereinafter referred to as 58 kDa and 88 kDa, respectively, or the 58 kDa and the 88 kDa component of MTP, respectively, or the low molecular weight subunit and the high molecular weight subunit of MTP, respectively.

Characterization of the 58,000 molecular weight component of bovine MTP indicates that it is the previously characterized multifunctional protein, protein disulfide isomerase (PDI). Wetterau et al., J. Biol. Chem. 265, 9800-7 (1990). The presence of PDI in the transfer protein

is supported by evidence showing that (1) the amino terminal 25 amino acids of the bovine 58,000 kDa component of MTP is identical to that of bovine PDI, and (2) disulfide isomerase activity was expressed by bovine MTP following the dissociation of the 58 kDa - 88 kDa protein complex. In addition, antibodies raised against bovine PDI, a protein which by itself has no TG transfer activity, were able to immunoprecipitate bovine TG transfer activity from a solution containing purified bovine MTP.

PDI normally plays a role in the folding and assembly of newly synthesized disulfide bonded proteins within the lumen of the endoplasmic reticulum. Bulleid & Freedman, Nature 335, 649-51 (1988). It catalyzes the proper pairing of cysteine residues into disulfide bonds, thus catalyzing the proper folding of disulfide bonded proteins. In addition, PDI has been reported to be identical to the beta subunit of human prolyl 4-hydroxylase. Koivu et al., J. Biol. Chem. 262, 6447-9 (1987). The role of PDI in the bovine transfer protein is not clear. It does appear to be an essential component of the transfer protein as dissociation of PDI from the 88 kDa component of bovine MTP by either low concentrations of a denaturant (guanidine HCl), a chaotropic agent (sodium perchlorate), or a nondenaturing detergent (octyl glucoside) results in a loss of transfer activity. Wetterau et al., Biochemistry 30, 9728-35 (1991). Isolated bovine PDI has no apparent lipid transfer activity, suggesting that either the 88 kDa polypeptide is the transfer protein or that it confers transfer activity to the protein complex.

The tissue and subcellular distribution of MTP activity in rats has been investigated. Wetterau & Zilversmit, Biochem. Biophys. Acta 875, 610-7 (1986). Lipid transfer activity was found in liver and intestine. Little or no transfer activity was found in plasma, brain, heart, or kidney. Within the liver, MTP was a soluble protein located within the lumen of the microsomal

fraction. Approximately equal concentrations were found in the smooth and rough microsomes.

Abetalipoproteinemia is an autosomal recessive disease characterized by a virtual absence of plasma lipoproteins which contain apolipoprotein B (apoB). Kane & Havel in The Metabolic Basis of Inherited Disease, Sixth edition, 1139-64 (1989). Plasma TG levels may be as low as a few mg/dL, and they fail to rise after fat ingestion. Plasma cholesterol levels are often only 20-45 mg/dL. These abnormalities are the result of a genetic defect in the assembly and/or secretion of very low density lipoproteins (VLDL) in the liver and chylomicrons in the intestine. The molecular basis for this defect has not been previously determined. In subjects examined, triglyceride, phospholipid, and cholesterol synthesis appear normal. At autopsy, subjects are free of atherosclerosis. Schaefer et al., Clin. Chem. 34, B9-12 (1988). A link between the apoB gene and abetalipoproteinemia has been excluded in several families. Talmud et al., J. Clin. Invest. 82, 1803-6 (1988) and Huang et al., Am. J. Hum. Genet. 46, 1141-8 (1990).

Subjects with abetalipoproteinemia are afflicted with numerous maladies. Kane & Havel, supra. Subjects have fat malabsorption and TG accumulation in their enterocytes and hepatocytes. Due to the absence of TG-rich plasma lipoproteins, there is a defect in the transport of fat-soluble vitamins such as vitamin E. This results in acanthocytosis of erythrocytes, spinocerebellar ataxia with degeneration of the fasciculus cuneatus and gracilis, peripheral neuropathy, degenerative pigmentary retinopathy, and ceroid myopathy. Treatment of abetalipoproteinemic subjects includes dietary restriction of fat intake and dietary supplementation with vitamins A, E and K.

In vitro, MTP catalyzes the transport of lipid molecules between phospholipid membranes. Presumably, it plays a similar role in vivo, and thus plays some role in lipid metabolism. The subcellular (lumen of the microsomal

fraction) and tissue distribution (liver and intestine) of MTP have led to speculation that it plays a role in the assembly of plasma lipoproteins, as these are the sites of plasma lipoprotein assembly. Wetterau & Zilversmit, Biochem. Biophys. Acta 875, 610-7 (1986). The ability of MTP to catalyze the transport of TG between membranes is consistent with this hypothesis, and suggests that MTP may catalyze the transport of TG from its site of synthesis in the endoplasmic reticulum (ER) membrane to nascent lipoprotein particles within the lumen of the ER.

Olofsson and colleagues have studied lipoprotein assembly in HepG2 cells. Bostrom et al., J. Biol. Chem. 263, 4434-42 (1988). Their results suggest small precursor lipoproteins become larger with time. This would be consistent with the addition or transfer of lipid molecules to nascent lipoproteins as they are assembled. MTP may play a role in this process. In support of this hypothesis, Howell and Palade, J. Cell Biol. 92, 833-45 (1982), isolated nascent lipoproteins from the hepatic Golgi fraction of rat liver. There was a spectrum of sizes of particles present with varying lipid and protein compositions. Particles of high density lipoprotein (HDL) density, yet containing apoB, were found. Higgins and Hutson, J. Lipid Res. 25, 1295-1305 (1984), reported lipoproteins isolated from Golgi were consistently larger than those from the endoplasmic reticulum, again suggesting the assembly of lipoproteins is a progressive event. However, there is no direct evidence in the prior art demonstrating that MTP plays a role in lipid metabolism or the assembly of plasma lipoprotein.

Recent reports (Science, Vol. 258, page 999, 1992; D. Sharp et al, Nature, Vol. 365, page 65, 1993) demonstrate that the defect causing abetalipoproteinemia is in the MTP gene, and as a result, the MTP protein. Individuals with abetalipoproteinemia have no MTP activity, as a result of mutations in the MTP gene, some of which have been characterized. These results indicate that MTP

is required for the synthesis of apoB containing lipoproteins, such as VLDL, the precursor to LDL. It therefore follows that inhibitors of MTP would inhibit the synthesis of VLDL and LDL, thereby lowering VLDL levels, LDL levels, cholesterol levels, and triglyceride levels in animals and man.

Canadian Patent Application No. 2,091,102 published March 2, 1994 (corresponding to U.S. application Serial No. 117,362, filed September 3, 1993 (file DC21b)) which is incorporated herein by reference), reports MTP inhibitors which also block the lipoproteins in a human hepatic cell line (HepG2 cells). This provides further support for the proposal that an MTP inhibitor would lower apoB containing lipoprotein and lipid levels in vivo. This Canadian patent application discloses a method for identifying the MTP inhibitors.

The use of microsomal triglyceride transfer protein (MTP) inhibitors for decreasing serum lipids including cholesterol and triglycerides and their use in treating atherosclerosis, obesity, hyperglycemia, and pancreatitis is disclosed in WO 96/26205, U.S. Application Serial No. 472,067, filed June 6, 1995 (file DC21e), U.S. Application Serial No. 548,811, filed January 11, 1996 (file DC21h), U.S. provisional application No. 60/017,224, filed May 9, 1996 (file HX79a*), U.S. provisional application No. 60/017,253, filed May 10, 1996 (file HX82*), U.S. provisional application No. 60/017,254, filed May 10, 1996 (file HX84*) and U.S. provisional appication No. 60/028,216, filed October 1, 1996 (file HX86*).

All of the above U.S. applications are incorporated herein by reference.

Description of the Invention

In accordance with the present invention, patients who may have (and preferably will have) one or more risk factors for a coronary and/or cerebrovascular event such as hypercholesterolemia and/or coronary heart disease

including previous myocardial infarction, who are treated with an MTP inhibitor alone or optionally in combination with another cholesterol lowering drug, for example, an HMG CoA reductase inhibitor, such as pravastatin, experience a rapid marked and significant reduction in cardiovascular events. Thus, although a certain number of patients having one or more risk factors for coronary or cerebrovascular events are expected to suffer a cardiovascular incident, such as a myocardial infarction and/or unstable angina and/or stroke, such patients when treated with an MTP inhibitor, alone or in combination with another cholesterol lowering drug, have a rapid and sizable reduction in such cardiovascular events.

Thus, in accordance with the present invention, a method is provided for preventing onset of or reducing risk of a cardiovascular event in a patient, which patient may have one or more risk factors for a coronary and/or cerebrovascular event, wherein a therapeutically effective amount of an MTP inhibitor by itself or optionally in combination with another cholesterol lowering drug such as an HMG CoA reductase inhibitor, is administered systemically, such as orally or parenterally or transdermally.

Preferred HMG CoA reductase inhibitors for use in combination with the MTP inhibitor are pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin and fluvastatin, more preferably pravastatin.

The term "risk factors for a coronary and/or cerebrovascular event" as employed herein refers to risk factors such as hypercholesterolemia, mixed hyperlipidemia, hyperlipoproteinemia, hypertriglyceridemia, coronary heart disease (CHD), coronary artery disease (CAD), family history of coronary artery disease, hypertension, diabetes, cigarette smoking, cerebrovascular disease and/or male gender.

The term "coronary heart disease" (CHD) as employed herein refers to diseases including atherosclerosis of the

coronary arteries, previous myocardial infarction, angina pectoris and/or heart failure.

The term "cerebrovascular disease" as employed herein refers to diseases including atherosclerosis of the intracranial and/or extracranial arteries, stroke, and transient ischemic attacks.

The term "cardiovascular event(s)" or "serious cardiovascular adverse event(s)" as employed herein refers to coronary and/or cerebrovascular event(s) including primary myocardial infarction, secondary myocardial infarction, angina pectoris (including unstable angina), congestive heart failure, sudden cardiac death, cerebral infarction, syncope, transient ischemic attack and the like.

In accordance with the method of the invention, where the risk factor in patients to be treated is hypercholesterolemia, the serum total cholesterol concentrations will be at least 5.2 mmol/liter (at least 200 mg/dl). The patients may also have other risk factors for atherosclerotic coronary artery disease such as hypertension, previous myocardial infarction, smoker and the like, with or without hypercholesterolemia or elevated cholesterol.

The method of the invention applies to treatment of patients with normal cholesterol (that is less than 200 mg/dl) to prevent or inhibit onset of a first myocardial infarction or to prevent or inhibit onset of a second myocardial infarction.

The method of the invention applies to patients with one or more of the above risk factors to prevent or inhibit onset of a first myocardial infarction or a second myocardial infarction or angina or a cerebral infarction or TIA or sycope.

The method of the invention also applies to inhibition or regression of coronary artery atherosclerosis in patients with or without risk factors.

Notwithstanding the above, it will be appreciated that in accordance with the present invention, the MTP inhibitor alone or in combination with another cholesterol lowering drug may be administered to patients irrespective of cholesterol levels and other risk factors to achieve the reduction in cardiovascular events.

Other cholesterol lowering drugs or drugs which are inhibitors of cholesterol biosynthesis which may be used in the method of the invention in combination with the MTP inhibitor include HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, bile acid sequestrants, probucol, niacin, niacin derivatives, neomycin, aspirin, and the like.

It is believed that the combination of MTP inhibitor and other cholesterol lowering drug, which works by a mechanism other than inhibiting MTP, is a surprising and unique concept in treating diseases involved with elevated cholesterol and/or triglycerides and atherosclerosis, in that the combination may provide additional anticholesterolemic effects over that which may be obtained using each of the components of the combination alone. It is expected that reduced levels of each of the MTP inhibitor and other cholesterol lowering drug may be employed to achieve desired results, albeit with reduced side effects.

Detailed Description of the Invention

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

The term "MTP" refers to a polypeptide or protein complex that (1) if obtained from an organism (e. g., cows, humans, etc.), can be isolated from the microsomal fraction of homogenized tissue; and (2) stimulates the transport of triglycerides, cholesterol esters, or phospholipids from synthetic phospholipid vesicles, membranes or lipoproteins to synthetic vesicles, membranes, or lipoproteins and which is distinct from the cholesterol ester transfer protein

[Drayna et al., Nature 327, 632-634 (1987)] which may have similar catalytic properties.

The phrase "stabilizing" atherosclerosis as used in the present application refers to slowing down the development of and/or inhibiting the formation of new atherosclerotic lesions.

The phrase "causing the regression of" atherosclerosis as used in the present application refers to reducing and/or eliminating atherosclerotic lesions.

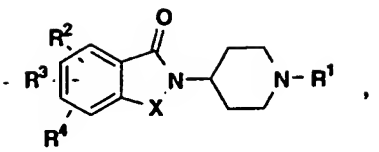
The combination of the MTP inhibitor and other cholesterol lowering drug will be employed in a weight ratio to each other of within the range of from about 1000:1 to about 0.001:1 and preferably from about 0.05:1 to about 100:1.

MTP inhibitors to be employed in the methods of the invention include MTP inhibitors disclosed in WO 96/26205 published August 29, 1996, Canadian Patent Application No. 2,091,102 (corresponding to U.S. Application Serial No. 117,362), U.S. Application Serial No. 472,067, filed June 6, 1995 (file DC21e), U.S. Application Serial No. 548,811, filed January 11, 1996 (file DC21h), U.S. provisional application No. 60/017,224, filed May 9, 1996 (file HX79a*), U.S. provisional application No. 60/017,253, filed May 10, 1996 (file HX82*), U.S. provisional application No. 60/017,254, filed May 10, 1996 (file HX84*) and U.S. provisional application No. 60/028,216, filed October 1, 1996 (file HX86*).

All of the above U.S. applications are incorporated herein by reference.

The MTP inhibitors disclosed in U.S. Application Serial No. 472,067, filed June 6, 1995 (file DC21e) are piperidine compounds of the structure

I.



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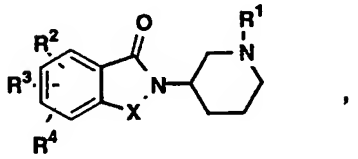
II.



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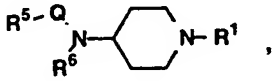
III.



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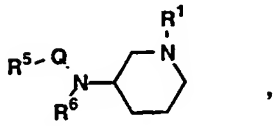

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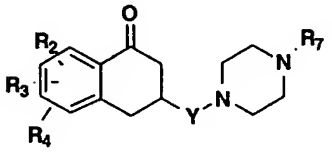
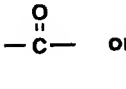
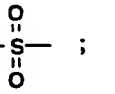
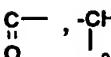
V.



where Q is  or  ;

X is: CHR^8,  , or ;

R^8, R^9 and R^{10} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

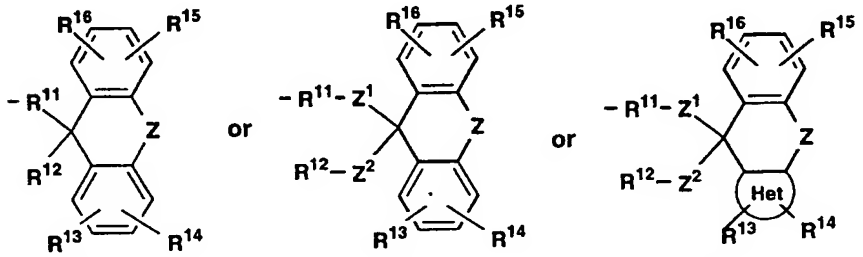
Y is $-(CH_2)_m-$ or 

wherein m is 2 or 3;

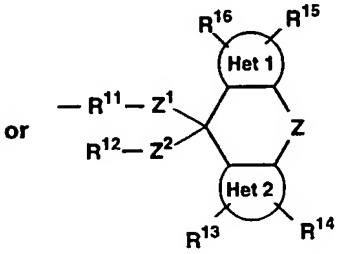
R^1 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl wherein alkyl has at least 2 carbons,

diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, diarylalkynyl, diarylalkylaryl, heteroarylalkyl wherein alkyl has at least 2 carbons, cycloalkyl, or cycloalkylalkyl wherein alkyl has at least 2 carbons, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, fluorenyl, heteroarylalkyl, hydroxy or oxo;

or R^1 is a fluorenyl-type group of the structure



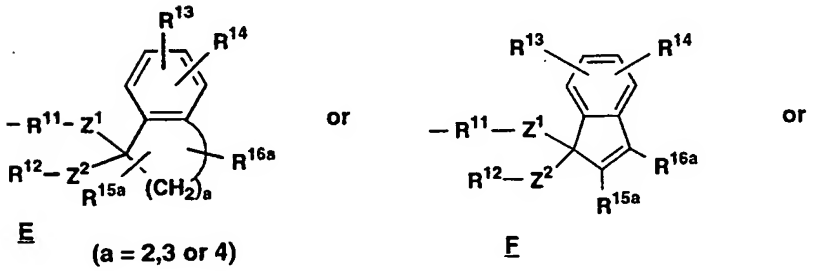
A B C



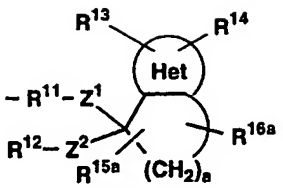
; or

D

R^1 is an indenyl-type group of the structure

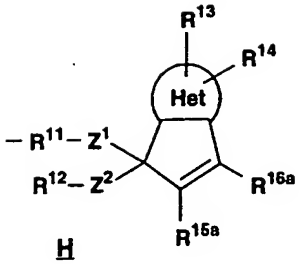


E (a = 2,3 or 4) F



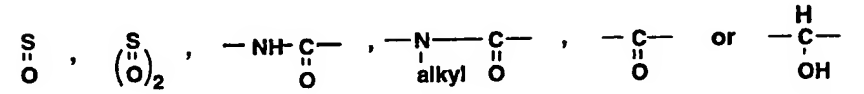
G

or

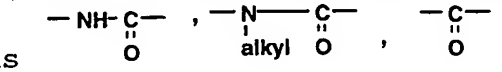


H ;

Z^1 and Z^2 are the same or different and are independently a bond, O, S,



with the proviso that with respect to B, at least one of Z^1 and Z^2 will be other than a bond; R^{11} is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms; arylene or mixed arylene-alkylene; R^{12} is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl, with the provisos in preferred compounds that

(1) when R^{12} is H, aryloxy, alkoxy or arylalkoxy, then Z^2 is 

or a bond and

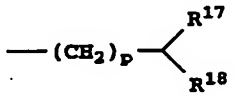
(2) when Z^2 is a bond, R^{12} cannot be heteroaryl or heteroarylalkyl;

Z is bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene from 1 to 5 carbon atoms; R^{13}, R^{14}, R^{15}, and R^{16} are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl or aryloxy;

R^{15a} and R^{16a} are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, alkoxy, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy,

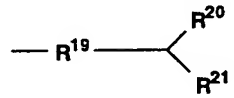
arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

or R^1 is a group of the structure



wherein p is 1 to 8 and R^{17} and R^{18} are each independently H, alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl at least one of R^{17} and R^{18} being other than H;

or R^1 is a group of the structure



wherein R^{19} is aryl or heteroaryl;

R^{20} is aryl or heteroaryl;

R^{21} is H, alkyl, aryl, alkylaryl, arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;

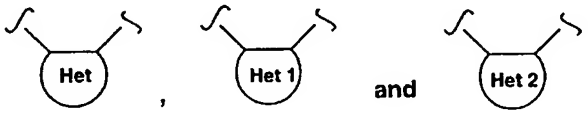
R^2, R^3, R^4 are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

R^5 is independently alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, heteroaryloxy, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, heteroarylcarbonyl, amino, alkylamino, arylamino, heteroarylamino, cycloalkyloxy, cycloalkylamino, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cyclohetero-alkylalkyl, aryl, heteroaryl, arylalkyl, arylcyclo-alkyl,

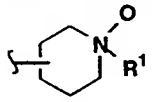
arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, alkylsulfinyl;

R^6 is hydrogen or C_1-C_4 alkyl or C_1-C_4 alkenyl; all optionally substituted with 1, 2, 3 or 4 groups which may independently be any of the substituents listed in the definition of R^5 set out above;

R^7 is alkyl, aryl or arylalkyl wherein alkyl by itself or as part of arylalkyl is optionally substituted with oxo (O) ;



are the same or different and are independently selected from heteroaryl containing 5- or 6-ring members; and

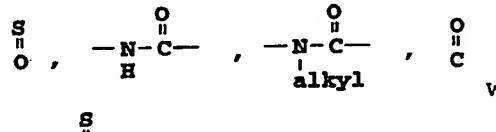


N-oxides thereof; and

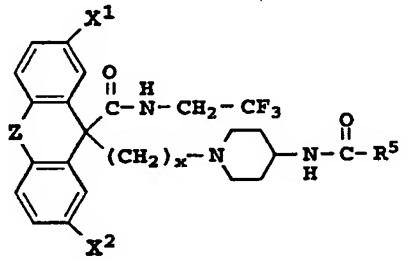
pharmaceutically acceptable salts thereof; with the provisos that preferably where in the first formula X is CH_2, and R^2, R^3 and R^4 are each H, then R^1 will be other than 3,3-diphenylpropyl, and preferably in the fifth formula, where one of R^2, R^3 and R^4 is 6-fluoro, and the others are H, R^7 will be other than 4-(2-methoxyphenyl).

In the MTP inhibitors disclosed in U.S. Application Serial No. 472,067, it is preferred that

(a) in the third and fourth formulas, where R^1 is indanyl E, if Z^1 is a bond, then R^{12}-Z^2 is other than alkyl or H; and

(b) in the third and fourth formulas, where R^1 is indenyl F, then Z^2 is  where Z^2 is other than alkoxy, or  where R^{12} is other than alkyl.

The MTP inhibitors disclosed in U.S. application Serial No. 548,811 filed January 11, 1996 (file DC21h), have the structure



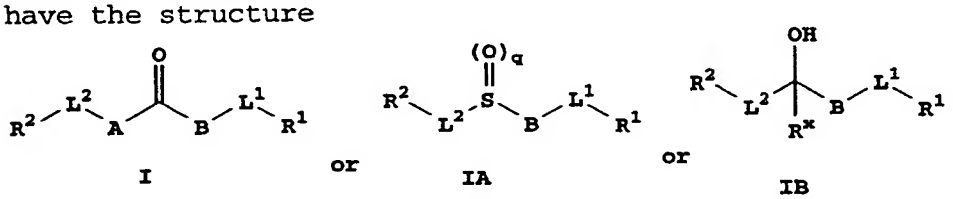
including the piperidine N-oxide thereof or a pharmaceutically acceptable salt thereof, wherein Z is a bond, O or S;

X^1 and X^2 are independently selected from H or halo;

x is an integer from 2 to 6;

R^5 is heteroaryl, aryl, heterocycloalkyl or cycloalkyl, each R^5 group being optionally substituted with 1, 2, 3 or 4 substituents which may be the same or different.

The MTP inhibitors disclosed in U.S. provisional application No. 60/017,224, filed May 9, 1996 (file HX79a*) have the structure

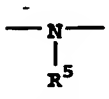


I or IA or IB

including pharmaceutically acceptable salts thereof, wherein q is 0, 1 or 2;

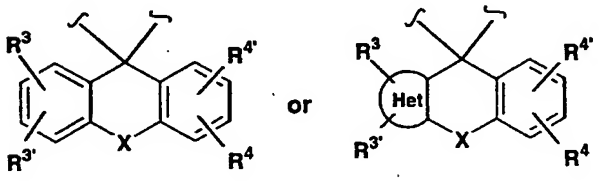
A is (1) a bond;

(2) -O- ; or

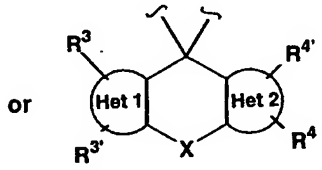
(3)  ;

where R^5 is H or lower alkyl or R^5 together with R^2 forms a carbocyclic or heterocyclic ring system containing 4 to 8 members in the ring.

B is a fluorenyl-type group of the structure:

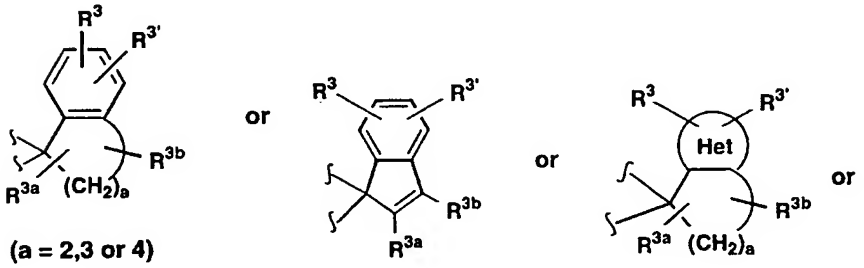


or

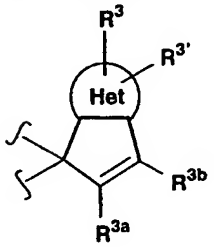


(the above B is also referred to as a fluorenyl- type ring or moiety); or

B is an indenyl-type group of the structure



(a = 2,3 or 4)



(the above B is also referred to as an indenyl-type ring or moiety);

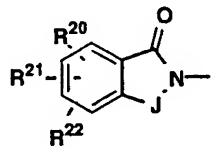
R^x is H, alkyl or aryl;

R^1 is alkyl, alkenyl, alkynyl, alkoxyl, (alkyl or aryl)$_3$Si (where each alkyl or aryl group is independent), cycloalkyl, cycloalkenyl, substituted alkylamino,

substituted arylalkylamino, aryl, arylalkyl, arylamino, aryloxy, heteroaryl, heteroarylamino, heteroaryloxy, arylsulfonylamino, heteroarylsulfonylamino, arylthio, arylsulfinyl, arylsulfonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, $-PO(R^{13})(R^{14})$, (where R^{13} and R^{14} are independently alkyl, aryl, alkoxy, aryloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, cycloheteroalkyl, cycloheteroalkylalkyl, cycloheteroalkoxy, or cycloheteroalkylalkoxy); R^1 can also be aminocarbonyl (where the amino may optionally be substituted with one or two aryl, alkyl or heteroaryl groups); cyano, 1,1-(alkoxyl or aryloxy)$_2$alkyl (where the two aryl or alkyl substituents can be independently defined, or linked to one another to form a ring, such as 1,3-dioxane or 1,3-dioxolane, connected to L^1 (or L^2 in the case of R^2) at the 2-position); 1,3-dioxane or 1,3-dioxolane connected to L^1 (or L^2 in the case of R^2) at the 4-position.

The R^1 group may have from one to four substituents, which can be any of the R^3 groups or R^1 groups, and any of the preferred R^1 substituents set out below.

R^1 may be substituted with the following preferred substituents: alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, heteroaryloxylcarbonylamino, uriedo (where the uriedo nitrogens may be substituted with alkyl, aryl or heteroaryl), heterocyclylcarbonylamino (where the heterocycle is connected to the carbonyl group via a nitrogen or carbon atom), alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino,



,

where J is: CHR^{23}, $-\overset{\overset{O}{\|}}{C}-$, $-\overset{R^{24}}{\underset{|}{CH}}-\overset{R^{25}}{\underset{|}{CH}}-$ or $-\overset{R^{24}}{\underset{|}{C}}=\overset{R^{25}}{\underset{|}{C}}-$;

R^{23}, R^{24} and R^{25} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

R^{20}, R^{21}, R^{22} are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl; and these preferred substituents may either be directly attached to R^1, or attached via an alkylene chain at an open position.

R^2 is the same or different from R^1 and is independently any of the groups set out for R^1, H, polyhaloalkyl (such as CF_3CH_2, $CF_3CF_2CH_2$ or CF_3) or cycloheteroalkyl, and may be substituted with one to four of any of the groups defined for R^3, or any of the substituents preferred for R^1.

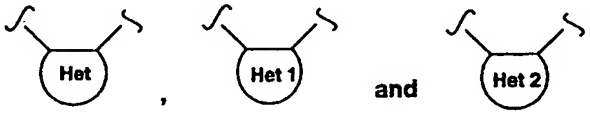
L^1 is a linking group containing from 1 to 10 carbons in a linear chain (including alkylene, alkenylene or alkynylene), which may contain, within the linking chain any of the following: one or two alkenes, one or two alkynes, an oxygen, an amino group optionally substituted with alkyl or aryl, an oxo group; and may be substituted with one to five alkyl or halo groups (preferably F).

L^2 may be the same or different from L^1 and may independently be any of the L^1 groups set out above or a singe bond.

R^3, $R^{3'}$, R^4 and $R^{4'}$ may be the same or different and are independently selected from H, halogen, CF_3, haloalkyl, hydroxy, alkoxy, alkyl, aryl, alkenyl, alkenyloxy, alkynyl, alkynyloxy, alkanoyl, nitro, amino, thiol, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxy, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, cycloheteroalkyl, cycloheteroalkylalkyl, cyano, Ar, Ar-alkyl, ArO, Ar-amino, Ar-thio, Ar-sulfinyl, Ar-sulfonyl, Ar-carbonyl, Ar-carbonyloxy or Ar-carbonylamino, wherein Ar

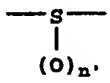
is aryl or heteroaryl and Ar may optionally include 1, 2 or 3 additional rings fused to Ar;

R^{3a} and R^{3b} are the same or different and are independently any of the R^3 groups except hydroxy, nitro, amino or thio;



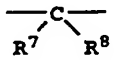
are the same or different and independently represent a 5 or 6 membered heteroaryl ring which may contain 1, 2, 3 or 4 heteroatoms in the ring which are independently N, S or O; and including N-oxides.

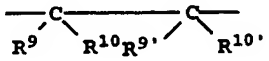
X (in the fluorenyl type ring) is a bond, or is one of the following groups:

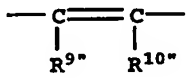
(1) 

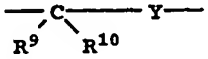
(2) -O-

(3) 

(4) 

(5) 

(6) 

(7) 

wherein

Y is O, N-R^6 or S;

n' is 0, 1 or 2;

R^6 is H, lower alkyl, aryl, -C(O)-R^{11} or -C(O)-O-R^{11};

R^7 and R^8 are the same or different and are independently H, alkyl, aryl, halogen, $-O-R^{12}$, or

R^7 and R^8 together can be oxygen to form a ketone;

R^9, R^{10}, $R^{9'}$ and $R^{10'}$ are the same or different and are independently H, lower alkyl, aryl or $-O-R^{11}$;

$R^{9''}$ and $R^{10''}$ are the same or different and are independently H, lower alkyl, aryl, halogen or $-O-R^{11}$;

R^{11} is alky or aryl;

R^{12} is H, alkyl or aryl.

The following provisos apply to preferred formula I compounds:

(a) when R^1 is unsubstituted alkyl or unsubstituted arylalkyl, L^1 cannot contain amino;

(b) when R^1 is alkyl, L^1 cannot contain amino and oxo in adjacent positions (to form an amido group);

(c) when R^2L^2A- is H_2N-, R^1L^1 cannot contain amino;

(d) when R^1 is cyano, L^1 must have more than 2 carbons;

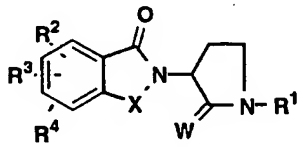
(e) R^1L^1 must contain at least 3 carbons.

With respect to compounds IA and IB, R^2L^2 cannot have an O or N atom directly attached to $S=(O)_q$ or $CR^x(OH)$, and for IA, R^2L^2 cannot be H.

With respect to preferred compounds IA and IB, where R^1 is cycloheteroalkyl, R^1 is exclusive of 1-piper-idinyl, 1-pyrrolidinyl, 1-azetidinyl or 1-(2-oxo-pyrrolidinyl).

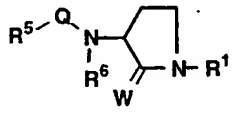
The MTP inhibitors disclosed in U.S. provisional application No. 60/017,253, filed May 10, 1996 (file HX82*) are pyrrolidine compounds and have the structure

I

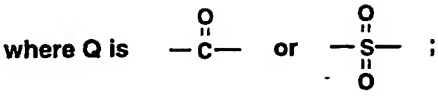


; or

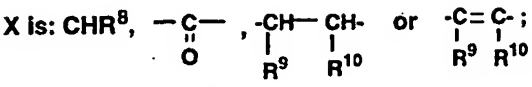
II



;

where Q is  ;

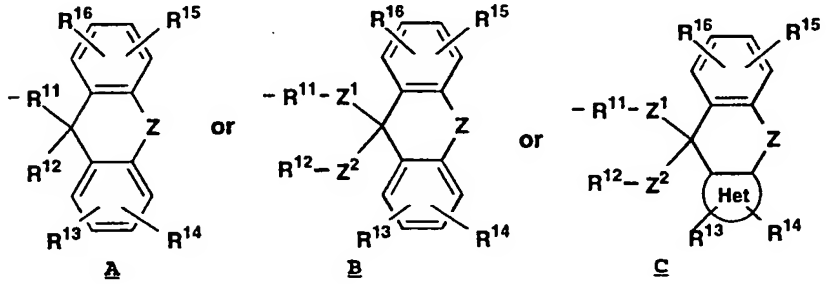
W is H,H or O;

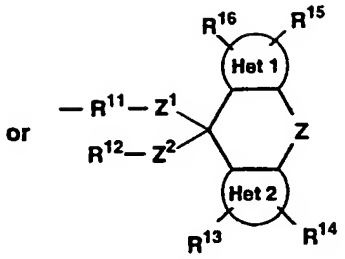
X is: CHR^8, 

R^8, R^9 and R^{10} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

R^1 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl (wherein alkyl preferably has at least 2 carbons, more preferably at least 3 carbons), diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, diarylalkynyl, diarylalkylaryl, heteroarylalkyl (wherein alkyl preferably has at least 2 carbons, more preferably at least 3 carbons), cycloalkyl, or cycloalkylalkyl (wherein alkyl preferably has at least 2 carbons, more preferably at least 3 carbons); all of the aforementioned R^1 groups being optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, fluorenyl, heteroarylalkyl, hydroxy or oxo; or

R^1 is a fluorenyl-type group of the structure

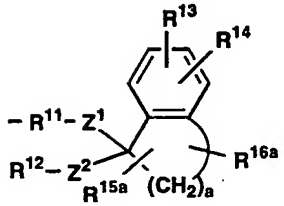




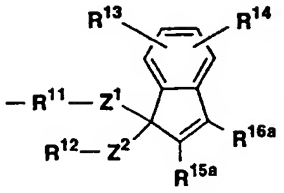
; or

D

R^1 is an indenyl-type group of the structure



or

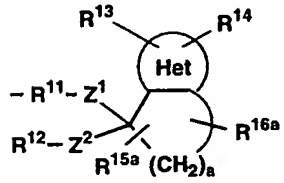


or

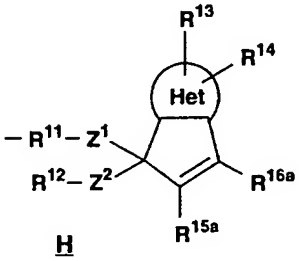
E

(a = 2,3 or 4)

F



or

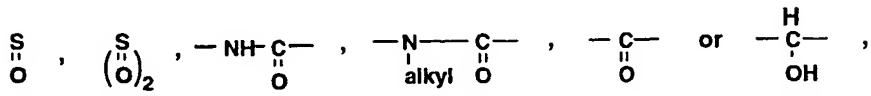


;

G

H

Z^1 and Z^2 are the same or different and are independently a bond, O, S,

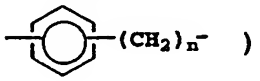


with the proviso that with respect to B, at least one of Z^1 and Z^2 will be other than a bond;

R^{11} is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms, arylene (for example

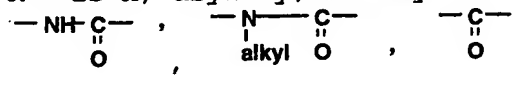
)

or mixed arylene-alkylene (for example



)

where n is 1 to 6;

R^{12} is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl; with the provisos that (1) when R^{12} is H, aryloxy, alkoxy or arylalkoxy, then Z^2 is  or a bond;

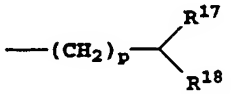
and (2) when Z^2 is a bond, R^{12} cannot be heteroaryl or heteroarylalkyl;

Z is a bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene of from 1 to 5 carbon atoms;

R^{13}, R^{14}, R^{15}, and R^{16} are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

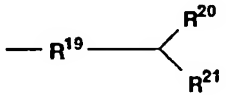
R^{15a} and R^{16a} are independently any of the R^{15} or R^{16} groups except hydroxy, nitro, amino or thio;

or R^1 is



wherein p is 1 to 8 and R^{17} and R^{18} are each independently H, alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl, at least one of R^{17} and R^{18} being other than H;

or R^1 is



wherein R^{19} is aryl or heteroaryl;

R^{20} is aryl or heteroaryl;

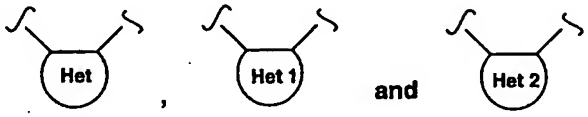
R^{21} is H, alkyl, aryl, alkylaryl, arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;

R^2, R^3, R^4 are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

R^5 is alkyl , alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloheteroalkyl, heteroaryloxy, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, heteroarylcarbonyl, amino, alkylamino, arylamino, heteroarylamino, cycloalkyloxy, cycloalkylamino, all of the R^5 substituents and R^6 substituents (set out hereinafter) being optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino (wherein the amino includes 1 or 2 substituents which are alkyl, aryl or heteroaryl, or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or alkylsulfinyl. Where R^5 is phenyl, aryl, heteroaryl or cycloalkyl; this group preferably includes an ortho hydrophobic substituent such as alkyl, haloalkyl (with up

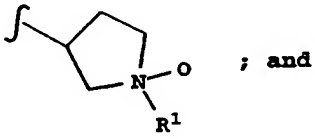
to 5 halo groups), alkoxy, haloalkoxy (with up to 5 halo groups), aryl, aryloxy or arylalkyl;

R^6 is hydrogen or C_1-C_4 alkyl or C_1-C_4 alkenyl;



are the same or different and are independently selected from heteroaryl containing 5- or 6-ring members; and

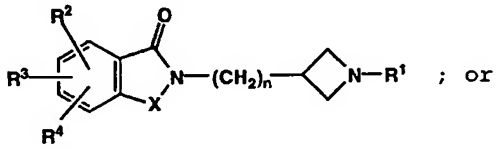
including N-oxides of the formulae I and II compounds, that is



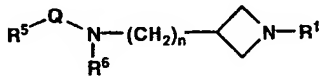
including pharmaceutically acceptable salts thereof.

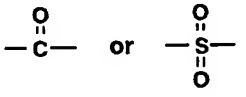
The MTP inhibitors disclosed in U.S. provisional application No. 60/017,254, filed May 10, 1996, (file HX84*) are azetidine compounds which have the structure

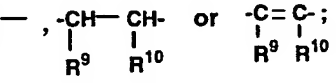
I



II



where Q is  ;

X is: CHR^8,  ;

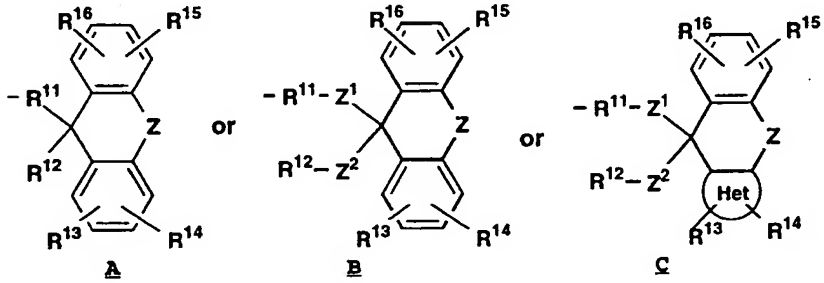
n is 0 or 1;

R^8, R^9 and R^{10} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

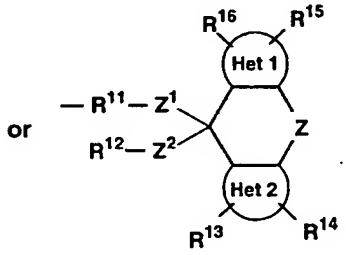
R^1 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl (wherein alkyl preferably has at least 2 carbons,

more preferably at least 3 carbons), diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, diarylalkynyl, diarylalkylaryl, heteroarylalkyl (wherein alkyl preferably has at least 2 carbons, more preferably at least 3 carbons), cycloalkyl, or cycloalkylalkyl (wherein alkyl preferably has at least 2 carbons, more preferably at least 3 carbons); all of the aforementioned R^1 groups being optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, fluorenyl, heteroarylalkyl, hydroxy or oxo; or

R^1 is a fluorenyl-type group of the structure

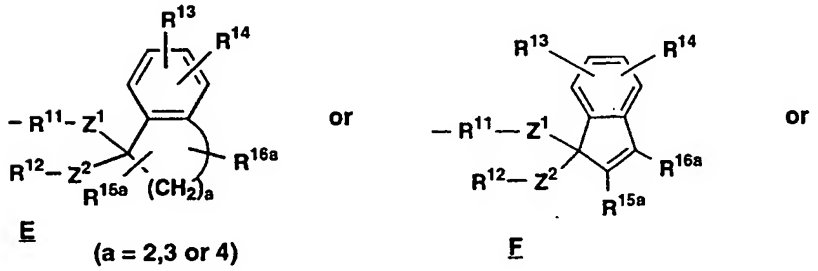


A B C

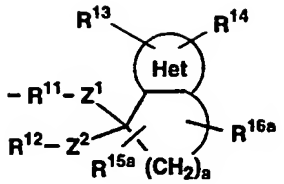


D ; or

R^1 is an indenyl-type group of the structure

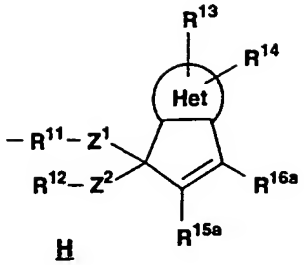


E (a = 2,3 or 4) F



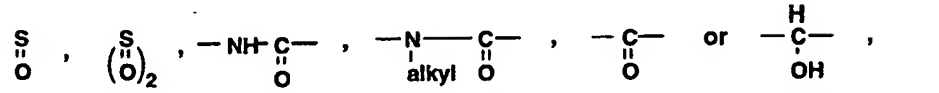
G

or



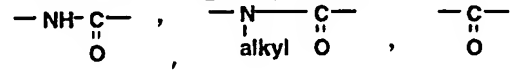
H ;

Z^1 and Z^2 are the same or different and are independently a bond, O, S,



with the proviso that with respect to B, at least one of Z^1 and Z^2 will be other than a bond;

R^{11} is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms, arylene (for example ), or mixed arylene-alkylene (for example ) where q is 1 to 6;

R^{12} is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl; with the provisos that (1) when R^{12} is H, aryloxy, alkoxy or arylalkoxy, then Z^2 is  or a bond;

and (2) when Z^2 is a bond, R^{12} cannot be heteroaryl or heteroarylalkyl;

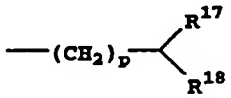
Z is a bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene of from 1 to 5 carbon atoms;

R^{13}, R^{14}, R^{15}, and R^{16} are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio,

aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

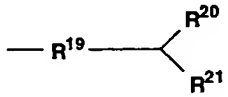
R^{15a} and R^{16a} are independently any of the R^{15} or R^{16} groups except hydroxy, nitro, amino or thio;

or R^1 is



wherein p is 1 to 8 and R^{17} and R^{18} are each independently H, alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl, at least one of R^{17} and R^{18} being other than H;

or R^1 is



wherein R^{19} is aryl or heteroaryl;

R^{20} is aryl or heteroaryl;

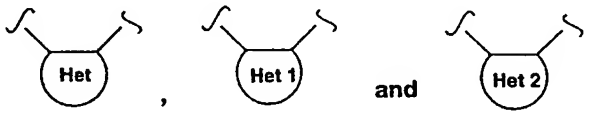
R^{21} is H, alkyl, aryl, alkylaryl, arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;

R^2, R^3, R^4 are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

R^5 is alkyl , alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloheteroalkyl, heteroaryloxy, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, heteroarylcarbonyl, amino, alkylamino, arylamino, heteroarylamino, cycloalkyloxy, cycloalkylamino, all of the R^5 substituents and R^6 substituents (set out hereinafter) being optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl,

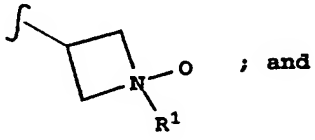
alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino (wherein the amino includes 1 or 2 substituents which are alkyl, aryl or heteroaryl, or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or alkylsulfinyl. Where R^5 is phenyl, aryl, heteroaryl or cycloalkyl; this group preferably includes an ortho hydrophobic substituent such as alkyl, haloalkyl (with up to 5 halo groups), alkoxy, haloalkoxy (with up to 5 halo groups), aryl, aryloxy or arylalkyl;

R^6 is hydrogen or C_1-C_4 alkyl or C_1-C_4 alkenyl;



are the same or different and are independently selected from heteroaryl containing 5- or 6-ring members; and

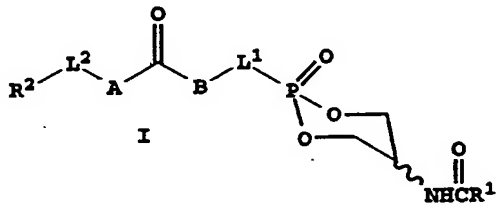
including N-oxides of the formulae I and II compounds, that is



; and

including pharmaceutically acceptable salts thereof.

The MTP inhibitors disclosed in U.S. provisional application Serial No. 60/028,216, filed October 1, 1996 (file HX86*) have the structure



I

including pharmaceutically acceptable salts thereof, wherein

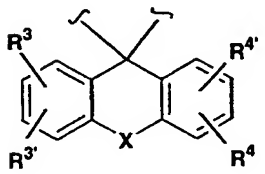
A is (1) a bond;

(2) -O- ; or

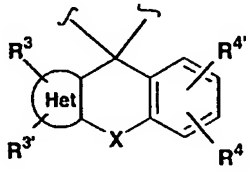
(3) ;

where R^5 is H or lower alkyl or R^5 together with R^2 forms a carbocyclic or heterocyclic ring system containing 4 to 8 members in the ring.

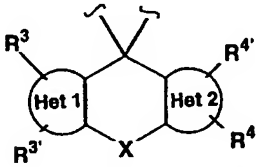
B is a fluorenyl-type group of the structure:



or

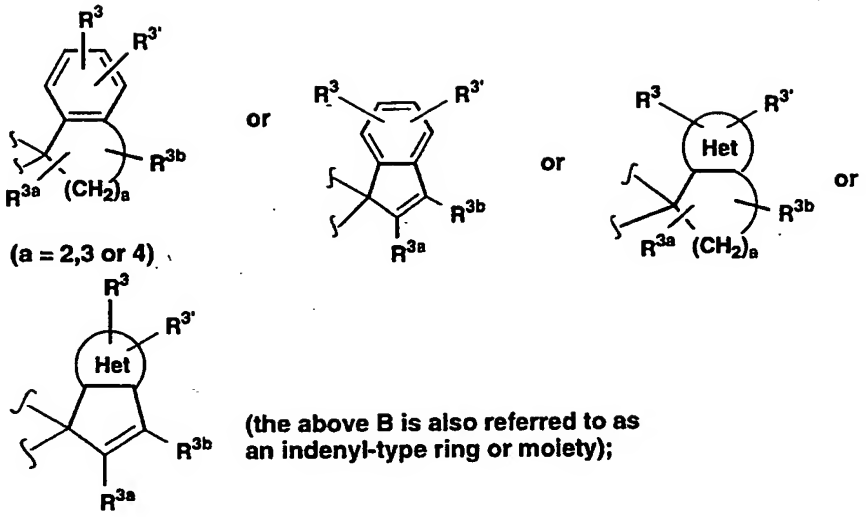


or



(the above B is also referred to as a fluorenyl- type ring or moiety); or

B is an indenyl-type group of the structure



(the above B is also referred to as an indenyl-type ring or moiety);

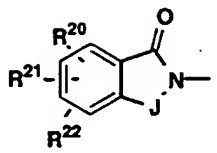
R^1 is independently alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, heteroaryloxy, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, heteroarylcarbonyl, amino, alkylamino, arylamino, heteroarylamino, cycloalkyloxy, cycloalkylamino, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino,

heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, alkylsulfinyl;

R^2 is alkyl, alkenyl, alkynyl, alkoxyl, (alkyl or aryl)$_3$Si (where each alkyl or aryl group is independent), cycloalkyl, cycloalkenyl, substituted alkylamino, substituted arylalkylamino, aryl, arylalkyl, arylamino, aryloxy, heteroaryl, heteroarylamino, heteroaryloxy, arylsulfonylamino, heteroarylsulfonylamino, arylthio, arylsulfinyl, arylsulfonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, -PO(R^{13})(R^{14}), (where R^{13} and R^{14} are independently alkyl, aryl, alkoxy, aryloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, cycloheteroalkyl, cycloheteroalkylalkyl, cycloheteroalkoxy, or cycloheteroalkylalkoxy); R^1 can also be aminocarbonyl (where the amino may optionally be substituted with one or two aryl, alkyl or heteroaryl groups); cyano, 1,1-(alkoxyl or aryloxy)$_2$alkyl (where the two aryl or alkyl substituents can be independently defined, or linked to one another to form a ring, such as 1,3-dioxane or 1,3-dioxolane, connected to L^1 (or L^2 in the case of R^2) at the 2-position); 1,3-dioxane or 1,3-dioxolane connected to L^1 (or L^2 in the case of R^2) at the 4-position.

The R^2 group may have from one to four substituents, which can be any of the R^3 groups or R^2 groups, and any of the preferred R^2 substituents set out below.

R^2 may be substituted with the following preferred substituents: alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, heteroaryloxylcarbonylamino, uriedo (where the uriedo nitrogens may be substituted with alkyl, aryl or heteroaryl), heterocyclylcarbonylamino (where the heterocycle is connected to the carbonyl group via a nitrogen or carbon atom), alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino,



where J is: CHR^{23}, $-\overset{O}{\overset{\|}{C}}-$, $-CH(R^{24})-CH(R^{25})-$ or $-C(R^{24})=C(R^{25})-$;

R^{23}, R^{24} and R^{25} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

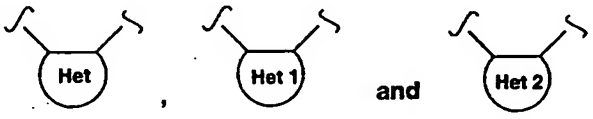
R^{20}, R^{21}, R^{22} are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl; and these preferred substituents may either be directly attached to R^1, or attached via an alkylene chain at an open position.

L^1 is a linking group containing from 1 to 10 carbons in a linear chain (including alkylene, alkenylene or alkynylene), which may contain, within the linking chain any of the following: one or two alkenes, one or two alkynes, an oxygen, an amino group optionally substituted with alkyl or aryl, an oxo group; and may be substituted with one to five alkyl or halo groups (preferably F).

L^2 may be the same or different from L^1 and may independently be any of the L^1 groups set out above or a singe bond.

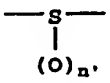
R^3, $R^{3'}$, R^4 and $R^{4'}$ may be the same or different and are independently selected from H, halogen, CF_3, haloalkyl, hydroxy, alkoxy, alkyl, aryl, alkenyl, alkenyloxy, alkynyl, alkynyloxy, alkanoyl, nitro, amino, thiol, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxy, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, cycloheteroalkyl, cycloheteroalkylalkyl, cyano, Ar, Ar-alkyl, ArO, Ar-amino, Ar-thio, Ar-sulfinyl, Ar-sulfonyl, Ar-carbonyl, Ar-carbonyloxy or Ar-carbonylamino, wherein Ar is aryl or heteroaryl and Ar may optionally include 1, 2 or 3 additional rings fused to Ar;

R^{3a} and R^{3b} are the same or different and are independently any of the R^3 groups except hydroxy, nitro, amino or thio;



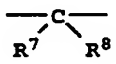
are the same or different and independently represent a 5 or 6 membered heteroaryl ring which may contain 1, 2, 3 or 4 heteroatoms in the ring which are independently N, S or O; and including N-oxides.

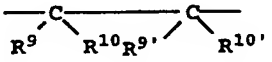
X (in the fluorenyl type ring) is a bond, or is one of the following groups:

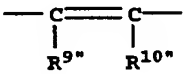
(1) 

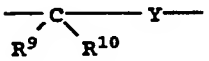
(2) -O-

(3) 

(4) 

(5) 

(6) 

(7) 

wherein

Y is O, N-R^6 or S;

n' is 0, 1 or 2;

R^6 is H, lower alkyl, aryl, -C(O)-R^{11} or -C(O)-O-R^{11};

R^7 and R^8 are the same or different and are independently H, alkyl, aryl, halogen, -O-R^{12}, or

R^7 and R^8 together can be oxygen to form a ketone;

R^9, R^{10}, $R^{9'}$ and $R^{10'}$ are the same or different and are independently H, lower alkyl, aryl or $-O-R^{11}$;

$R^{9''}$ and $R^{10''}$ are the same or different and are independently H, lower alkyl, aryl, halogen or $-O-R^{11}$;

R^{11} is alky or aryl;

R^{12} is H, alkyl or aryl.

Compounds disclosed as preferred in each of the above applications are preferred for use in the present invention.

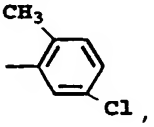
Most preferred MTP inhibitors to be employed in accordance with the present invention include preferred MTP inhibitors as set out in U.S. patent application Serial No. 548,811, filed January 11, 1996 (file DC21h) and in U.S. provisional application No. 60/017,224, filed May 9, 1996 (file HX79a*).

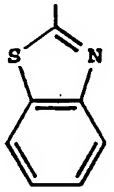
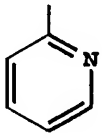
Thus, preferred compounds in U.S. patent application Serial No. 548,811 (file DC21h) for use herein are compounds

where Z is a bond;

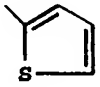
X^1 and X^2 are H;

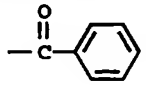
R^5 is aryl such as phenyl substituted with

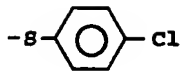
(1) aryl such as phenyl,  ,  ,

(2) heteroaryl such as  ,  ,

(3) halo such as Cl

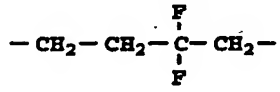
R^5 is heteroaryl such as  or  substituted with

(1) aroyl such as  ,

(2) arylthio such as 

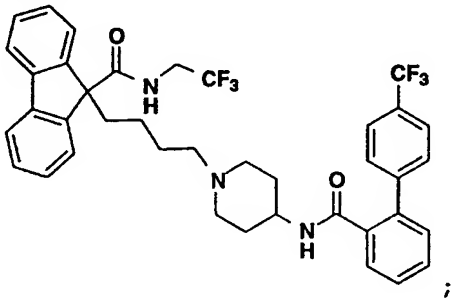
wherein the R^5 substituent is preferably in the position adjacent to the carbon linked to .

$(CH_2)_x$ is $-(CH_2)_4-$ or



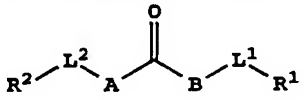
Most preferred is

9-[4-[4-[[2-(2,2,2-Trifluoroethoxy)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



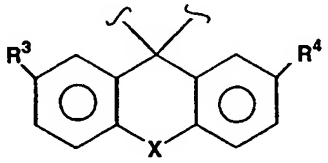
;

Preferred compounds in U.S. provisional application No. 60/017,224 (file HX79a*) for use herein are MTP inhibitor compounds of formula I that is



wherein A is NH,

B is



X is a bond, oxygen or sulfur; R^3 and R^4 are independently H or F.

Preferred R^1 groups are aryl, preferably phenyl, heteroaryl, preferably imidazoyl or pyridyl (preferably substituted with one of the preferred R^1 substituents: arylcarbonylamino, heteroarylcarbonylamino,

cycloalkylcarbonylamino, alkoxycarbonylamino, alkylsulfonylamino, arylsulfonylamino, heteroaryl-sulfonylamino), $PO(OAlkyl)_2$, heteroarylthio, benzthiazole-2-thio, imidazole-2-thio, alkyl, or alkenyl, cycloalkyl such as cyclohexyl, or 1,3-dioxan-2-yl.

Preferred R^2 groups are alkyl, polyfluoroalkyl (such as 1,1,1-trifluoroethyl), alkenyl, aryl or heteroaryl (preferably substituted with one of the preferred R^1 substituents above), or $PO(OAlkyl)_2$.

If R^2 is alkyl, 1,1,1-trifluoroethyl, or alkenyl, it is preferred that R^1 is other than alkyl or alkenyl.

It is preferred that L^1 contains 1 to 5 atoms in the linear chain and L^2 is a bond or lower alkylene.

Preferred embodiments of formula IA and formula IB compounds of the invention include those where B, L^1, L^2, R^1 and R^2 are as set out with respect to the preferred embodiments of the formula I compounds, q is 0 or 2 and R^x is H.

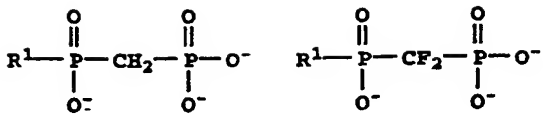
The other cholesterol lowering drug to be used in combination with the MTP inhibitor in accordance with the present invention is preferably an HMG CoA reductase inhibitor.

The HMG CoA reductase inhibitors suitable for use herein include, but are not limited to, mevastatin and related compounds as disclosed in U.S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds as disclosed in U.S. Patent No. 4,231,938, pravastatin and related compounds such as disclosed in U.S. Patent No. 4,346,227, simvastatin and related compounds as disclosed in U.S. Patent Nos. 4,448,784 and 4,450,171, with pravastatin, lovastatin or simvastatin being preferred. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluvastatin, cerivastatin, atorvastatin, pyrazole analogs of mevalonolactone derivatives as disclosed in U.S. Patent No. 4,613,610, indene analogs of mevalonolactone derivatives as disclosed in PCT application WO 86/03488, 6-[2-

(substituted-pyrrol-1-yl)alkyl]pyran-2-ones and derivatives thereof as disclosed in U.S. Patent No. 4,647,576, Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives as disclosed in French Patent No. 2,596,393, 2,3-di-substituted pyrrole, furan and thiophene derivatives as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone as disclosed in U.S. Patent No. 4,686,237, octahydronaphthalenes such as disclosed in U.S. Patent No. 4,499,289, keto analogs of mevinolin (lovastatin) as disclosed in European Patent Application No. 0,142,146 A2, as well as other known HMG CoA reductase inhibitors.

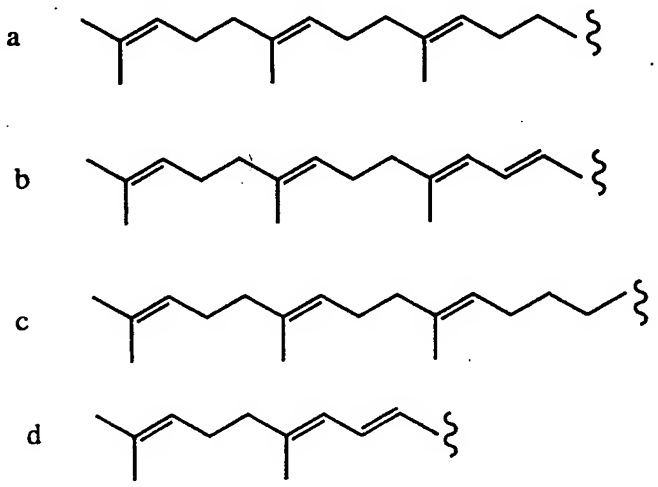
In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase suitable for use herein are disclosed in GB 2205837.

The squalene synthetase inhibitors suitable for use herein include, but are not limited to, α-phosphono-sulfonates disclosed in U.S. application Serial No. 08/266,888, filed July 5, 1994 (HX59b), those disclosed by Biller et al, J. Med. Chem. 1988, Vol. 31, No. 10, pp 1869-1871, including isoprenoid (phosphinylmethyl)phosphonates such as those of the formula



I II

R^1



including the triacids thereof, triesters thereof and tripotassium and trisodium salts thereof as well as other squalene synthetase inhibitors disclosed in U.S. Patent Nos. 4,871,721 and 4,924,024 and in Biller et al, J. Med. Chem., 1988, Vol. 31, No. 10, pp 1869 to 1871.

In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid pyrophosphates disclosed by P. Ortiz de Montellano et al, J. Med. Chem.; 1977, 20, 243-249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, J. Am. Chem. Soc. 1976, 98, 1291-1293, phosphinylphosphonates reported by McClard, R.W. et al, J.A.C.S., 1987, 109, 5544 and cyclopropanes reported by Capson, T.L., PhD dissertation, June, 1987, Dept. Med. Chem. U. of Utah, Abstract, Table of Contents, pp. 16, 17, 40-43, 48-51, Summary.

Preferred are pravastatin, lovastatin, atorvastatin, fluvastatin, cerivastatin or simvastatin.

All of the above U.S. applications are incorporated herein by reference.

Other cholesterol lowering drugs suitable for use herein include, but are not limited to, antihyperlipoproteinemic agents such as fibric acid derivatives, such as fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate, clinofibrate and the like, probucol, and related compounds as disclosed in U.S. Patent No. 3,674,836, probucol and gemfibrozil being preferred, bile acid sequestrants such as cholestyramine, colestipol and DEAE-Sephadex (Secholex®, Polidexide®), as well as clofibrate, lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphosphorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives), nicotinic acid, acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives such as disclosed in U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.

In carrying out the method of the present invention, the MTP inhibitor alone or in combination with the other cholesterol lowering drug may be administered to mammalian species, such as monkeys, dogs, cats, rats, humans, etc., and, as such, may be incorporated in a conventional systemic dosage form, such as a tablet, capsule, elixir or injectable. The above dosage forms will also include the necessary carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mennitol), anti-oxidants (ascorbic acid of sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral forms are quite satisfactory as well.

The dose administered must be carefully adjusted according to age, weight and condition of the patient, as well as the route of administration, dosage form and regimen and the desired result.

For oral administration, a satisfactory result may be obtained employing the MTP inhibitor in an amount within the range of from about 0.01 mg/kg to about 100 mg/kg and preferably from about 0.1 mg/kg to about 75 mg/kg one to four times daily.

A preferred oral dosage form, such as tablets or capsules, will contain the MTP inhibitor in an amount of from about 1 to about 500 mg, preferably from about 10 to about 400 mg, and more preferably from about 20 to about 250 mg one to four times daily.

For parenteral administration, the MTP inhibitor will be employed in an amount within the range of from about 0.005 mg/kg to about 10 mg/kg and preferably from about 0.005 mg/kg to about 8 mg/kg one to four times daily.

For oral administration, a satisfactory result may be obtained employing the HMG CoA reductase inhibitor in dosages employed, for example, for pravastatin, simvastatin, fluvastatin, lovastatin, atorvastatin or cerivastatin as indicated in the Physician's Desk Reference, such as in an amount within the range of from about 1 to 2000 mg, and preferably from about 4 to about 200 mg. The squalene synthetase inhibitor may be employed in dosages in an amount within the range of from about 10 mg to about 2000 mg and preferably from about 25 mg to about 200 mg.

A preferred oral dosage form, such as tablets or capsules, will contain MTP inhibitor in an amount of from about 1 to about 400 mg, and the HMG CoA reductase inhibitor in an amount of from about 0.1 to about 100 mg, preferably from about 5 to about 80 mg, and more preferably from about 10 to about 50 mg.

The other serum cholesterol lowering drugs when present will be employed in dosages normally employed as

indicated in the Physician's Desk Reference, for each of such agents such as in an amount within the range of from about 2 mg to about 7500 mg and preferably from about 2 mg to about 4000 mg.

The MTP inhibitor and other cholesterol lowering agent may be employed together in the same oral dosage form or in separate oral dosage forms taken at the same time.

The compositions described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily. It may be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

Tablets of various sizes can be prepared, e.g., of about 2 to 2000 mg in total weight, containing one or both of the active substances in the ranges described above, with the remainder being a physiologically acceptable carrier of other materials according to accepted pharmaceutical practice. These tablets can, of course, be scored to provide for fractional doses. Gelatin capsules can be similarly formulated.

Liquid formulations can also be prepared by dissolving or suspending one or the combination of active substances in a conventional liquid vehicle acceptable for pharmaceutical administration so as to provide the desired dosage in one to four teaspoonsful.

Such dosage forms can be administered to the patient on a regimen of one to four doses per day.

According to another modification, in order to more finely regulate the dosage schedule, the active substances may be administered separately in individual dosage units at the same time or carefully coordinated times. Since blood levels are built up and maintained by a regulated schedule of administration, the same result is achieved by the simultaneous presence of the two substances. The respective substances can be individually formulated in separate unit dosage forms in a manner similar to that described above.

Fixed combinations of MTP inhibitor and other cholesterol lowering drug are more convenient and are preferred, especially in tablet or capsule form for oral administration.

In formulating the compositions, the active substances, in the amounts described above, are compounded according to accepted pharmaceutical practice with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in the particular type of unit dosage form.

Illustrative of the adjuvants which may be incorporated in tablets are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as dicalcium phosphate or cellulose; a disintegrating agent such as corn starch, potato starch, alginic acid or the like; a lubricant such as stearic acid or magnesium stearate; a sweetening agent such as sucrose, aspartame, lactose or saccharin; a flavoring agent such as orange, peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets or capsules may be coated with shellac, sugar or both. A syrup of elixir may contain the active compound, water, alcohol or the like as the carrier, glycerol as solubilizer, sucrose as sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange.

Some of the active substances described above form commonly known, pharmaceutically acceptable salts such as alkali metal and other common basic salts or acid addition salts, etc. References to the base substances are therefore intended to include those common salts known to be substantially equivalent to the parent compound.

The formulations as described above will be administered for a prolonged period, that is, for as long

as the potential for elevated cholesterol and/or triglycerides and/or atherosclerosis and other diseases set out above remains or the symptoms continue. Sustained release forms of such formulations which may provide such amounts biweekly, weekly, monthly and the like may also be employed. A dosing period of at least one to two weeks are required to achieve minimal benefit.

The following Examples represent preferred embodiments of the present invention.

Examples 1 and 2

Formulations suitable for oral administration are prepared as described below.

Capsules each containing about 1 mg MTP inhibitor BMS 201,038 (Example 1) and capsules each containing about 5 mg BMS 201,038 (Example 2) are produced form the following ingredients.

Ingredient	Example 1 Amount (mg/ Capsule)	Example 2 Amount (mg/ Capsule)
BMS-201038 (1)	1.1	5.0
Lactose, Hydrous, NF	ca. 30.2	ca. 99.9
Lactose, Anhydrous NF	47.3	0.0
Microcrystalline Cellulose, NF	100.0	50.0
Pregelatinized Starch, NF	5.0	25.0
Sodium Starch Glycolate, NF	5.0	12.5
Colloidal Silicon Dioxide, NF	1.0	5.0
Magnesium Stearate, NF	0.3	0.6
Purified Water, USP or	q.s.	q.s.
Water for Injection, USP	q.s.	q.s.
Gray, Opaque, Size #0 Capsule Shell	One Capsule	One Capsule
Total Fill Weight	about 100.0	about 200.0

(1) In Example 1, this amount is expressed in terms of the amount of methane sulfonic acid salt per capsule at 100% potency. In Example 2, this amount is expressed in terms of free base. This is equivalent to 1 mg and 5 mg (Examples 1 and 2, respectively) of the free base.

The MTP inhibitor BMS 201,038, and colloidal silicon dioxide are blended in a suitable blender with lactose hydrous, microcrystalline cellulose, pregelatinized starch and a portion of sodium starch glycolate. The resulting blend is wet granulated with water. The wet granulation is dried in a suitable dryer. The remaining portion of sodium starch glycolate is added to the granulation and mixed therein. Magnesium stearate is added to the granulation and mixed therein. The resulting blend is filled into capsules.

Example 3

Pravastatin tablets (10, 20 or 40 mg as described in the 1996 PDR) and MTP inhibitor (BMS 201,238) tablets may be administered as a combination in accordance with the teachings of the present invention. In addition, the pravastatin and MTP inhibitor tablets may be ground up into powders and used together in a single capsule.

Example 4

Tablets containing 500 mg clofibrate by itself or in combination with 10 mg BMS 201,038 may be employed in separate dosage forms or combined in a single capsule form.

Examples 5, 6 and 7

Ciprofibrate, bezafibrate, gemfibrozil alone or in combination with an MTP inhibitor may also be prepared in a manner described hereinbefore in Examples 1 to 3.

What is claimed is:

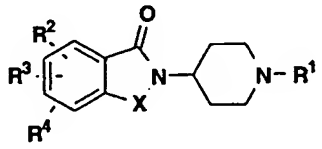
1. A method for preventing or reducing the risk of a cardiovascular event in a patient who may have one or more risk factors for a coronary and/or cerebrovascular event, which comprises administering to a patient in need of such treatment a therapeutically effective amount of an inhibitor of microsomal triglyceride transfer protein (MTP).

2. The method as defined in Claim 1 wherein the MTP inhibitor is employed alone.

3. The method as defined in Claim 1 wherein the MTP inhibitor is employed in combination with another cholesterol lowering drug.

4. The method as defined in Claim 1 wherein the MTP inhibitor has the structure

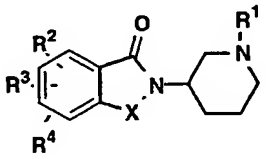
I.



,

or

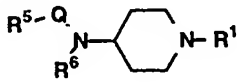
II.



,

or

III.



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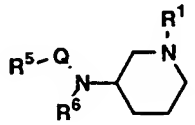
or

IV.



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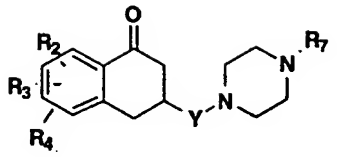
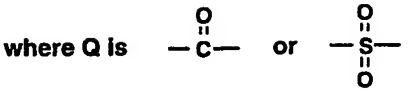
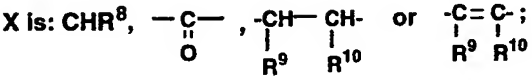
or

V. 

where Q is  ;

X is: CHR^8,  ;

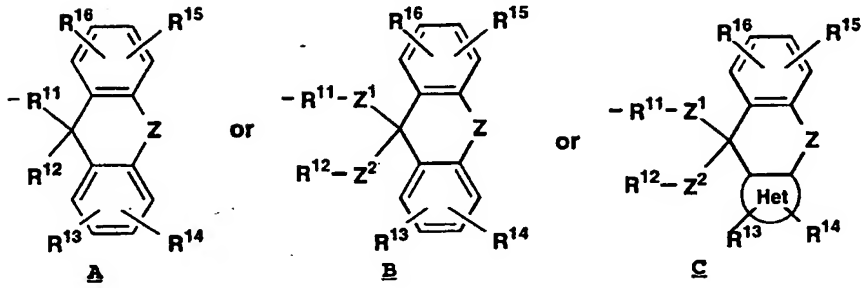
R^8, R^9 and R^{10} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

Y is $-(CH_2)_m-$ or 

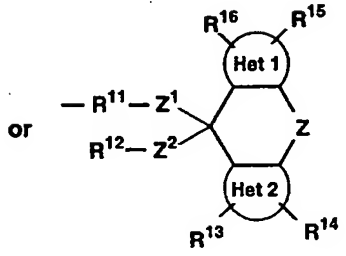
wherein m is 2 or 3;

R^1 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl wherein alkyl has at least 2 carbons, diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, diarylalkynyl, diarylalkylaryl, heteroarylalkyl wherein alkyl has at least 2 carbons, cycloalkyl, or cycloalkylalkyl wherein alkyl has at least 2 carbons, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, fluorenyl, heteroarylalkyl, hydroxy or oxo;

or R^1 is a fluorenyl-type group of the structure

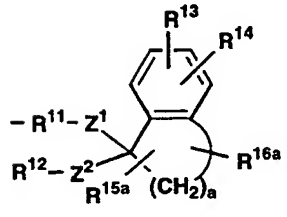


A B C

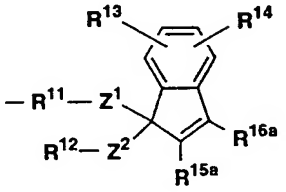


D ; or

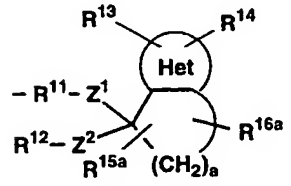
R^1 is an indenyl-type group of the structure



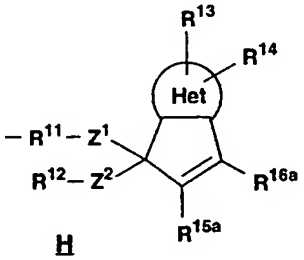
E (a = 2,3 or 4)



F

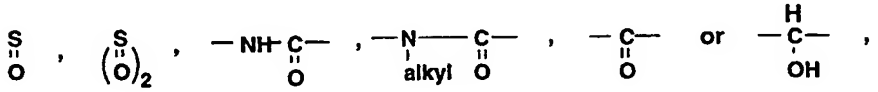


G



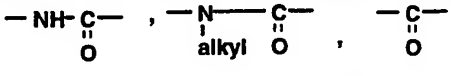
H ;

Z^1 and Z^2 are the same or different and are independently a bond, O, S,



,

with the proviso that with respect to B, at least one of Z^1 and Z^2 will be other than a bond; R^{11} is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms; arylene or mixed arylene-alkylene; R^{12} is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl, with the provisos that

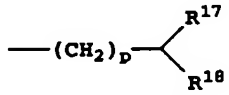
(1) when R^{12} is H, aryloxy, alkoxy or arylalkoxy, then Z^2 is  or a bond and

(2) when Z^2 is a bond, R^{12} cannot be heteroaryl or heteroarylalkyl;

Z is bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene from 1 to 5 carbon atoms; R^{13}, R^{14}, R^{15}, and R^{16} are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl or aryloxy;

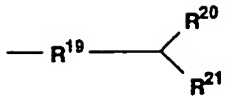
R^{15a} and R^{16a} are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, alkoxy, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

or R^1 is a group of the structure



wherein p is 1 to 8 and R^{17} and R^{18} are each independently H, alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl at least one of R^{17} and R^{18} being other than H;

or R^1 is a group of the structure



wherein R^{19} is aryl or heteroaryl;

R^{20} is aryl or heteroaryl;

R^{21} is H, alkyl, aryl, alkylaryl, arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;

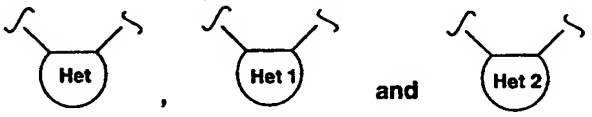
R^2, R^3, R^4 are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

R^5 is independently alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, heteroaryloxy, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, heteroarylcarbonyl, amino, alkylamino, arylamino, heteroarylamino, cycloalkyloxy, cycloalkylamino, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino,

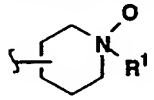
heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, alkylsulfinyl;

R^6 is hydrogen or C_1-C_4 alkyl or C_1-C_4 alkenyl; all optionally substituted with 1, 2, 3 or 4 groups which may independently be any of the substituents listed in the definition of R^5 set out above;

R^7 is alkyl, aryl or arylalkyl wherein alkyl by itself or as part of arylalkyl is optionally substituted with oxo $\left(\overset{O}{\overset{\|}{}}\right)$;



are the same or different and are independently selected from heteroaryl containing 5- or 6-ring members; and

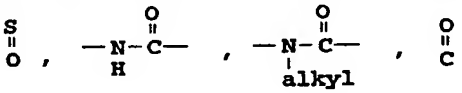


N-oxides thereof; and

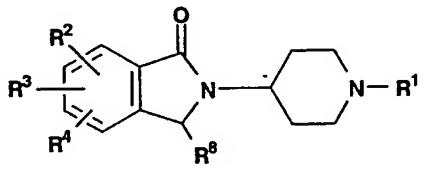
pharmaceutically acceptable salts thereof.

5. The method as defined in Claim 1 where in the compound administered,

(a) in the third and fourth formulas, where R^1 is indanyl E, if Z^1 is a bond, then R^{12}-Z^2 is other than alkyl or H; and

(b) in the third and fourth formulas, where R^1 is indenyl F, then Z^2 is  where Z^2 is other than alkoxy, or $\overset{S}{\overset{\|}{(O)_2}}$ where R^{12} is other than alkyl.

6. The method as defined in Claim 4 wherein the MTP inhibitor has the formula



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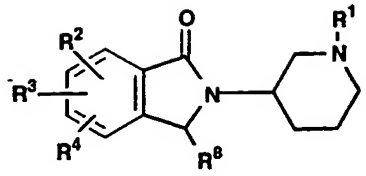
or



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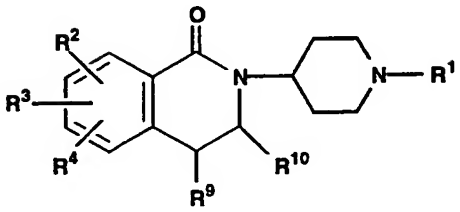
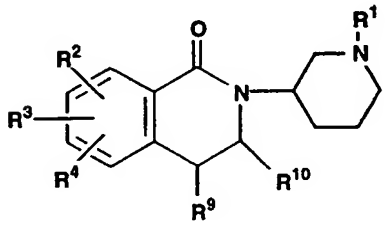
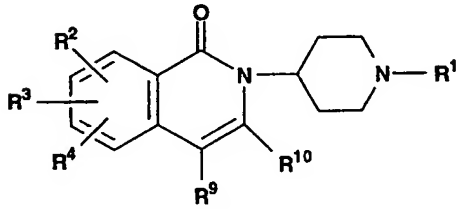


or



or



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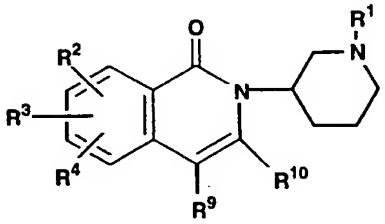

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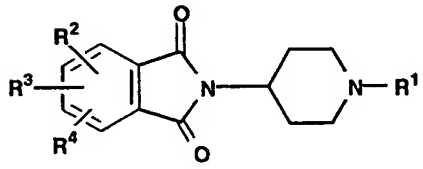

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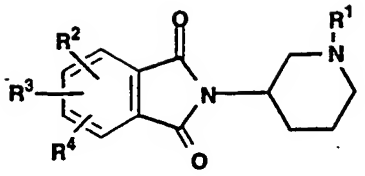
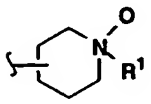
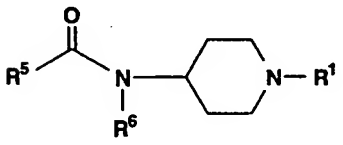




the N-oxides thereof and pharmaceutically acceptable salts thereof.

7. The method as defined in Claim 6 wherein the MTP inhibitor has the formula



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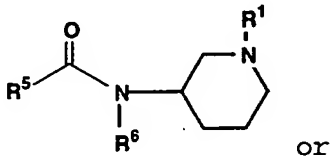

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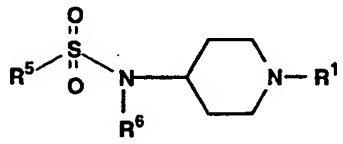
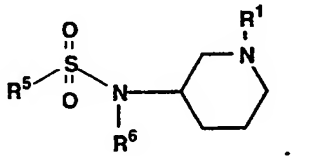
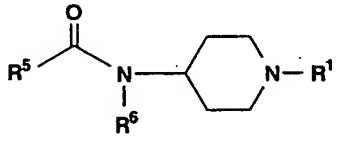


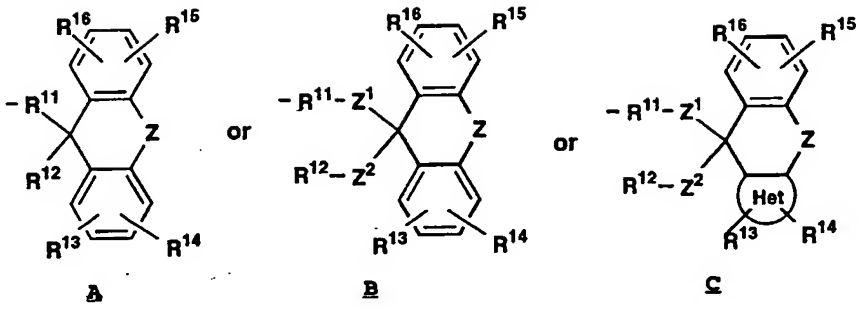
or



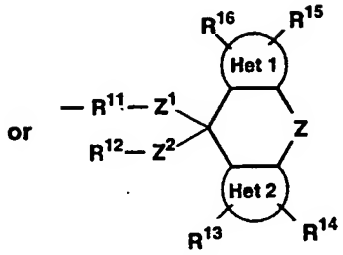
8. The method as defined in Claim 7 wherein the MTP inhibitor has the formula



9. The method as defined in Claim 4 where in the MTP inhibitor R^1 is

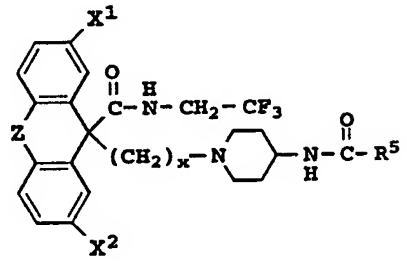


A or B or C



D

10. The method as defined in Claim 1 wherein the MTP inhibitor has the structure



including the piperidine N-oxide thereof or a pharmaceutically acceptable salt thereof, wherein Z is a bond, O or S;

X^1 and X^2 are independently selected from H or halo;

x is an integer from 2 to 6;

R^5 is heteroaryl, aryl, heterocycloalkyl or cycloalkyl, each R^5 group being optionally substituted with 1, 2, 3 or 4 substituents which may be the same or different.

11. The method as defined in Claim 10 where in the MTP inhibitor Z is a bond.

12. The method as defined in Claim 10 where the MTP inhibitor is a piperidine N-oxide.

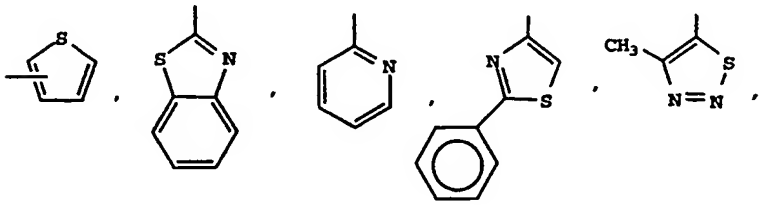
13. The method as defined in Claim 10 where in the MTP inhibitor $(CH_2)_x$ is optionally substituted with 1, 2 or 3 substituents which are the same or different and are alkyl or halo.

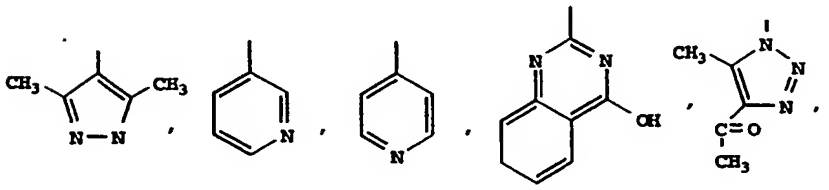
14. The method as defined in Claim 10 where in the MTP inhibitor R^5 is substituted with 1, 2, 3 or 4 substituents which may be the same or different and are halogen, monocyclic heteroaryl, bicyclic heteroaryl, heteroarylalkyl, cycloheteroalkyl, alkyl, alkoxy, cycloalkyl, aryl, aryloxy, substituted aryl, arylalkyloxy, heteroaryloxy, amino, alkylamino, alkyl(aryl)amino, heteroarylamino, arylamino, alkylthio, arylthio, arylthioalkyl, heteroarylthio, arylsulfinyl or acyl.

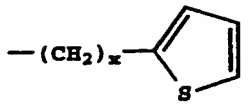
15. The method as defined in Claim 14 where in the MTP inhibitor the R^5 includes a substituent attached to a carbon in the position adjacent to the carbon linked to .

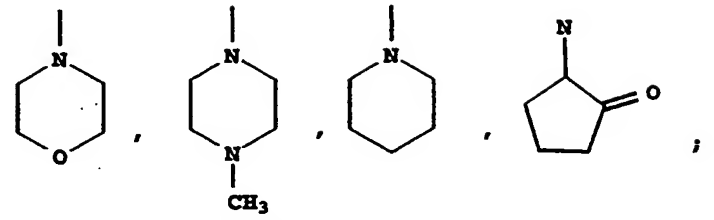
16. The method as defined in Claim 14 where in the MTP inhibitor R^5 is substituted with 1, 2, 3 or 4 of one or more of the following

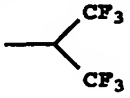
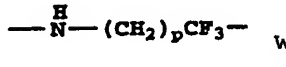
I, Cl, F, CF_3

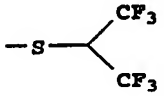


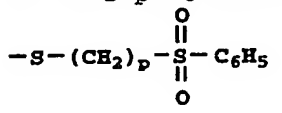
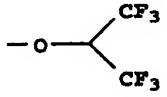


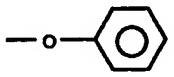
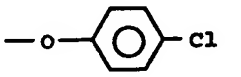

where x is 1 to 5

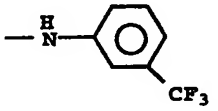
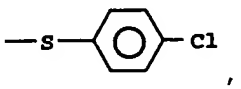
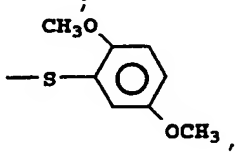


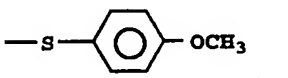
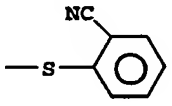
alkyl, phenyl, phenyl substituted with halo, alkyl, CF_3O, alkoxy,  , CF_3, or phenyl;  where p is 1 to 5, $-N(CH_3)C_6H_5$;


$-S-(CH_2)_pCF_3$ where p is 1 to 5, , -S-alkyl,

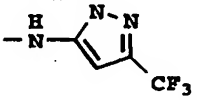

, $-O-(CH_2)_p-CF_3$,  , OCH_3;

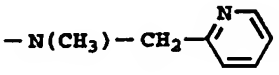

, 
cyclohexyl, ;

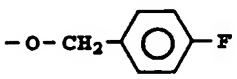
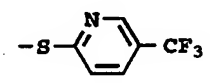
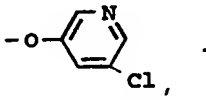
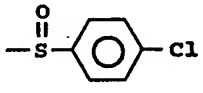
amino, 


,



;

alkanoyl, alkoxycarbonyl, aroyl, heteroarylaminocarbonyl, arylalkyloxycarbonyl,

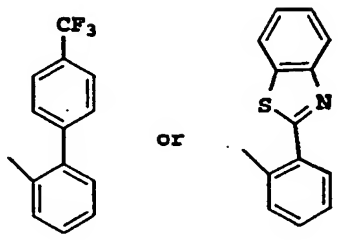

$-CH_2-S-C_6H_5$, ,


;

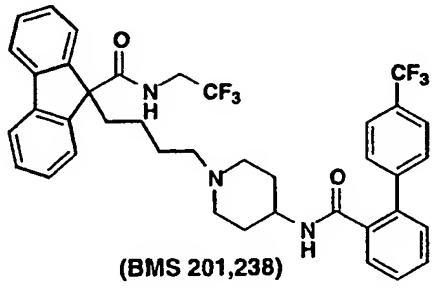

, 
, 
, 
.

17. The method as defined in Claim 16 where in the MTP inhibitor R^5 is phenyl substituted with haloalkylphenyl or heteroaryl.

18. The method as defined in Claim 17 where in the MTP inhibitor R^5 is

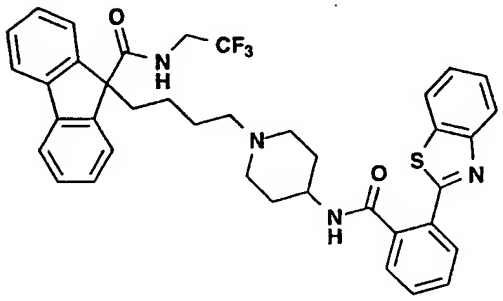


19. The method as defined in Claim 16 where in the MTP inhibitor is

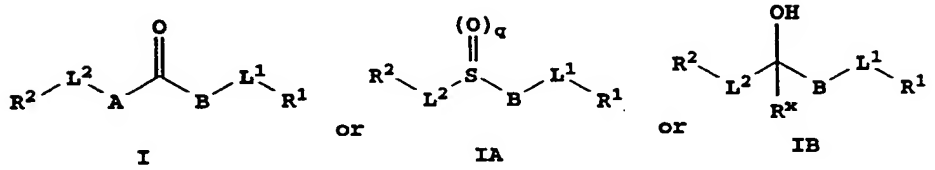


(BMS 201,238)

or



20. The method as defined in Claim 1 wherein the MTP inhibitor has the structure



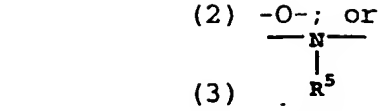
I IA IB

including pharmaceutically acceptable salts thereof, N-oxides thereof,

wherein q is 0, 1 or 2;

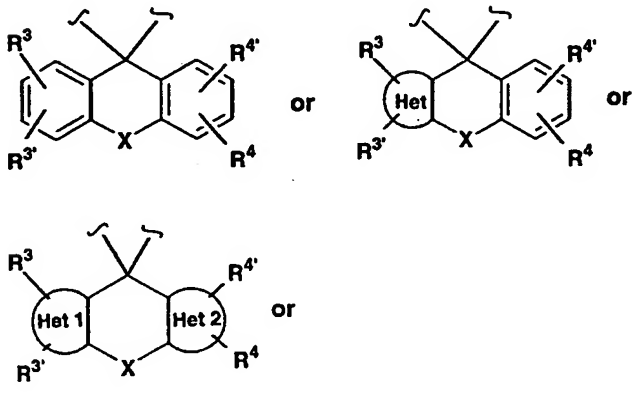
A is (1) a bond;

(2) -O-; or

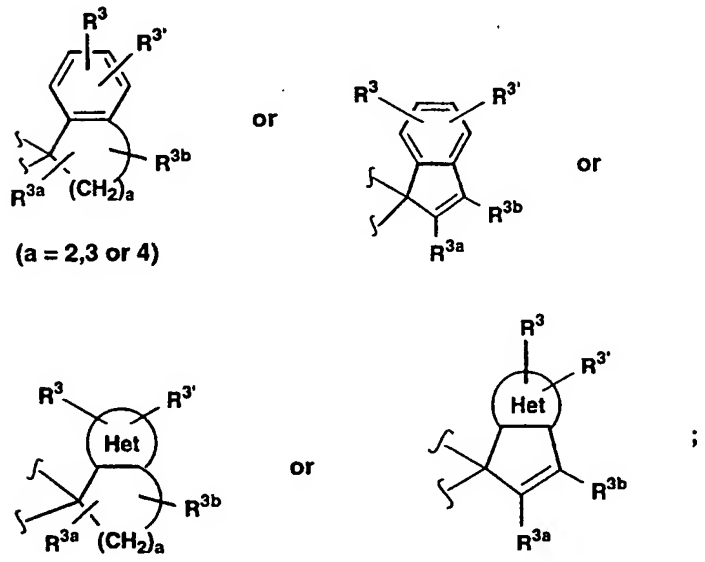
(3) 

where R^5 is H or lower alkyl, or R^5 together with R^2 forms a carbocyclic or heterocyclic ring system containing 4 to 8 members in the ring;

B is a fluorenyl-type group of the structure



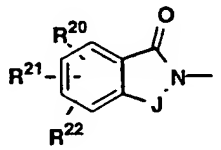
B is an indenyl-type group of the structure



R^x is H, alkyl or aryl;

R^1 is alkyl, alkenyl, alkynyl, alkoxyl, (alkyl or aryl)$_3$Si (where each alkyl or aryl group is independent),

cycloalkyl, cycloalkenyl, substituted alkylamino, substituted arylalkylamino, aryl, arylalkyl, arylamino, aryloxy, heteroaryl, heteroarylamino, heteroaryloxy, arylsulfonylamino, heteroarylsulfonylamino, arylthio, arylsulfinyl, arylsulfonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, $-PO(R^{13})(R^{14})$, (where R^{13} and R^{14} are independently alkyl, aryl, alkoxy, aryloxy, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, cycloheteroalkyl, cycloheteroalkylalkyl, cycloheteroalkoxy, or cycloheteroalkylalkoxy); aminocarbonyl (where the amino may optionally be substituted with one or two aryl, alkyl or heteroaryl groups); cyano, 1,1-(alkoxyl or aryloxy)$_2$alkyl (where the two aryl or alkyl substituents can be independently defined, or linked to one another to form a ring connected to L^1 (or L^2 in the case of R^2) at the 2-position); 1,3-dioxane or 1,3-dioxolane connected to L^1 (or L^2 in the case of R^2) at the 4-position; the R^1 group may optionally be substituted with 1, 2, 3 or 4 substituents, which can be any of the R^3 or R^1 groups or alkylcarbonylamino, cycloalkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxycarbonylamino, aryloxycarbonylamino, heteroaryloxylcarbonylamino, uriedo (where the uriedo nitrogens may optionally be substituted with alkyl, aryl or heteroaryl), heterocyclylcarbonylamino (where the heterocycle is connected to the carbonyl group via a nitrogen or carbon atom), alkylsulfonylamino, arylsulfonylamino, heteroarylsulfonylamino,



where J is: CHR^{23}, $-\overset{\overset{O}{\|}}{C}-$, $-CH(R^{24})-CH(R^{25})-$ or $-C(R^{24})=C(R^{25})-$;

R^{23}, R^{24} and R^{25} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

R^{20}, R^{21}, R^{22} are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl; and these substituents may either be directly attached to R^1, or attached via an alkylene at an open position;

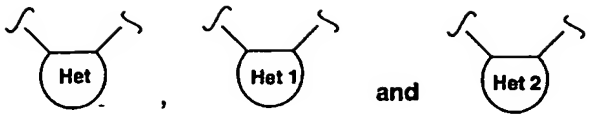
R^2 is independently any of the groups set out for R^1, H, polyhaloalkyl, or cycloheteroalkyl, and may be optionally substituted with one to four of any of the groups defined for R^3 or substituents defined for R^1;

L^1 is a linking group containing from 1 to 10 carbons in a linear chain including alkylene, alkenylene or alkynylene, which may contain, within the linking chain any of the following: one or two alkenes, one or two alkynes, an oxygen, an amino group, an oxo group, and may be substituted with one to five alkyl or halo groups;

L^2 may be the same or different from L^1 and may independently be any of the L^1 groups set out above or a singe bond;

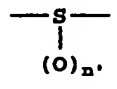
R^3, $R^{3'}$, R^4 and $R^{4'}$ may be the same or different and are independently selected from H, halogen, CF_3, haloalkyl, hydroxy, alkoxy, alkyl, aryl, alkenyl, alkenyloxy, alkynyl, alkynyloxy, alkanoyl, nitro, amino, thiol, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxy, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, cycloheteroalkyl, cycloheteroalkylalkyl, cyano, Ar-, Ar-alkyl, ArO, Ar-amino, Ar-thio, Ar-sulfinyl, Ar-sulfonyl, Ar-carbonyl, Ar-carbonyloxy or Ar-carbonylamino, wherein Ar is aryl or heteroaryl and Ar may optionally include 1, 2 or 3 additional rings fused to Ar;

R^{3a} and R^{3b} are the same or different and are independently any of the R^3 groups except hydroxy, nitro, amino or thio;

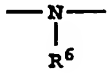


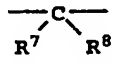
are the same or different and independently represent a 5 or 6 membered heteroaryl ring which contains 1, 2, 3 or 4 heteroatoms in the ring which are independently N, S or O; and including N-oxides;

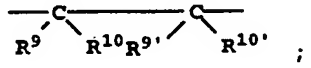
X is a bond, or is one of the following groups:

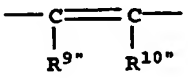
(1)  ;

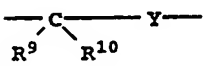
(2) -O- ;

(3)  ;

(4)  ;

(5)  ;

(6)  ; or

(7) 

wherein

Y is O, N-R^6 or S;

n' is 0, 1 or 2;

R^6 is H, lower alkyl, aryl, -C(O)-R^{11} or -C(O)-O-R^{11};

R^7 and R^8 are the same or different and are independently H, alkyl, aryl, halogen, -O-R^{12}, or

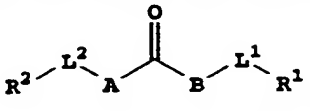
R^7 and R^8 together can be oxygen to form a ketone;

R^9, R^{10}, $R^{9'}$ and $R^{10'}$ are the same or different and are independently H, lower alkyl, aryl or -O-R^{11};

R^{9*} and R^{10*} are the same or different and are independently H, lower alkyl, aryl, halogen or $-O-R^{11}$;

R^{11} is alky or aryl;

R^{12} is H, alkyl or aryl.

21. The method as defined in Claim 20 wherein the MTP inhibitor has the structure  .

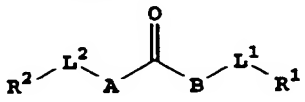
22. The method as defined in Claim 21 wherein A is a bond.

23. The method as defined in Claim 21 wherein A is -O-.

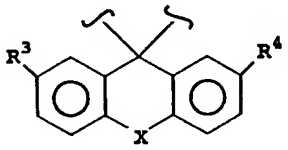
24. The method as defined in Claim 21 wherein A is  .

25. The method as defined in Claim 21 wherein B is a fluorenyl-type group.

26. The method as defined in Claim 21 wherein the MTP inhibitor has the formula



wherein B is



A is NH;

X is a bond, oxygen or sulfur;

R^3 and R^4 are the same or different and are H or F;

R^1 is aryl, phenyl, heteroaryl, imidazolyl, pyridyl, cyclohexyl, $PO(R^{13})(R^{14})$, heteroarylthio, benzthiazole-2-thio, imidazole-2-thio, alkyl, alkenyl or 1,3-dioxan-2-yl, wherein each of the above is optionally substituted;

R^2 is alkyl, polyfluoroalkyl, alkenyl, aryl, phenyl, heteroaryl, imidazolyl or pyridyl, wherein each of the above is optionally substituted;

L^1 is a chain containing 1 to 5 atoms in a linear chain;

L^2 is a bond or lower alkylene.

27. The method as defined in Claim 3 wherein the other cholesterol lowering drug is an inhibitor of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase.

28. The method as defined in Claim 27 wherein said inhibitor of the enzyme HMG CoA reductase is lovastatin, pravastatin, simvastatin, atorvastatin, fluvastatin or cerivastatin.

29. The method as defined in Claim 3 wherein the other cholesterol lowering drug is an inhibitor of the enzyme squalene synthetase.

30. The method as defined in Claim 3 wherein the other cholesterol lowering drug is a fibric acid derivative which is gemfibrozil, fenofibrate, clofibrate, bezafibrate, ciprofibrate or clinofibrate.

31. The method as defined in Claim 3 wherein the other cholesterol lowering drug is probucol, gemfibrozil, clofibrate, dextrothyroxine or its sodium salt, colestipol or its hydrochloride, cholestyramine, nicotinic acid, neomycin, p-aminosalicylic acid or aspirin.

32. The method as defined in Claim 3 wherein the MTP inhibitor is present in a weight ratio to said other cholesterol lowering drug of within the range of from about 0.001:1 to about 1000:1.

33. The method as defined in Claim 3 wherein the MTP inhibitor is BMS 201,038, employed alone or with a cholesterol lowering drug which is pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin or cerivastatin.

34. The method as defined in Claim 1 wherein the patient to be treated has one or more risk factors which includes hypercholesterolemia, mixed hyperlipidemia, hyperlipoproteinemia, hypertriglyceridemia, coronary heart disease, coronary artery disease, family history of

coronary artery disease, hypertension, diabetes, cigarette smoking, cerebrovascular disease and/or male gender.

35. The method as defined in Claim 1 wherein the patient to be treated has hypercholesterolemia.

36. The method as defined in Claim 1 wherein the patient has normal cholesterol and previous myocardial infarction and a second mycardial infarction is prevented.

37. The method as defined in Claim 1 wherein the patient to be treated has normal cholesterol and a first myocardial infarction is prevented.

38. The method as defined in Claim 1 wherein treatment results in reduction or inhibition of onset of primary myocardial infarction.

39. The method as defined in Claim 1 wherein treatment results in reduction or inhibition of onset of secondary myocardial infarction.

40. The method as defined in Claim 1 wherein treatment results in reduction or inhibition of onset of cerebral infarction, TIA or syncope.

41. The method as defined in Claim 1 wherein the treatment causes a reduction or inhibition of onset of primary myocardial infarction, secondary myocardial infarction, angina, cerebral infarction, TIA and/or syncope.

42. The method as defined in Claim 1 wherein the treatment causes inhibition or regression of coronary artery atherosclerosis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/00524

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/445, 31/235, 31/22
US CL : 514/325, 532, 546

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/325, 532, 546

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN: compounds and methods of use

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,346,227 A (TERAHARA ET AL) 24 August 1982, See entire document.	1-42
Y	US 3,674,836 A (CREGER) 04 July 1972, See entire document.	1-42
Y	EPO 0 643 057 A (BRISTOL-MEYERS SQUIBB COMPANY) 15 March 1995, See entire document	1-42

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"B"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 25 APRIL 1998	Date of mailing of the international search report 28 MAY 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Deborah Reese /DR RUSSELL TRAVERS Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*